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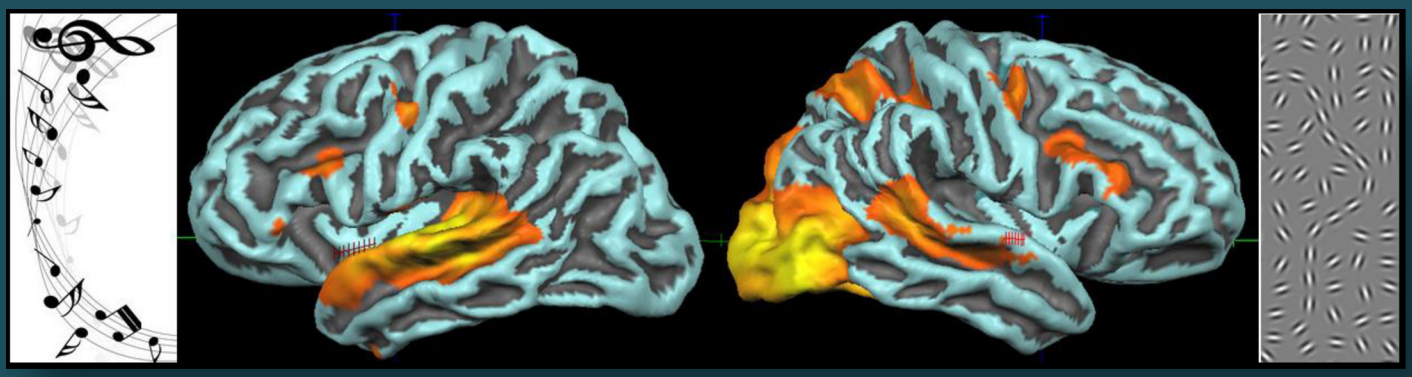

Dysfunctions of visual and auditory Gestalt perception (amusia) after stroke

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Behavioral correlates and functional magnetic resonance imaging

Stephanie Heike Rosemann

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Stephanie Heike Rosemann

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List of Publications

All publications used in this cumulative dissertation are marked with (*). The articles have been published in or submitted to international scientific journals.

Articles in Referenced Journals

(*) **Rosemann, S.**, Brunner, F., Kastrup, A., & Fahle, M. (submitted to *Journal of the Neurological Sciences*). Musical, visual and cognitive deficits after middle cerebral artery infarction.

(*) **Rosemann, S.**, Erhard, P., & Fahle, M. (submitted to *Music Perception*). Amusia after stroke – an fMRI study.

(*) **Rosemann, S.**, Erhard, P., & Fahle, M. (submitted to *Music Perception*). Lateralization of music perception in healthy elderly people – an fMRI study.

Rosemann, S., Wefel, I., Elis, V., & Fahle, M. (submitted to *Graefe's Archive for Clinical and Experimental Ophthalmology*). Audio-visual interaction in visual motion detection.

Rosemann, S., Altenmüller, E., & Fahle, M. (2015). The art of sight-reading: Influence of practice, playing tempo, complexity and cognitive skills on the eye–hand span in pianists *Psychology of Music*, doi:10.1177/0305735615585398.

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(*) **Rosemann, S.**, Erhard, P., & Fahle, M. (2015). Two amusic stroke patients: Behavior and imaging results. Program No. 137.14. 2015 Neuroscience Meeting Planner. Washington, DC: Society for Neuroscience, 2015. Online

(*) **Rosemann, S**., Brunner, F., Kastrup, A., & Fahle, M. (2015). Deficits in visual and auditory Gestalt perception after stroke. ECVP Abstract Supplement, page 189.

Rosemann, S., Altenmüller, E., Trenner, D., & Fahle, M. (2013). Sight-reading in skilled pianists: Eye-hand span is independent of practice but associated with the musicians' cognitive abilities. Perception 42, ECVP Abstract Supplement, page 133.

Poster Presentations

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Rosemann, S., Altenmüller, E., Trenner, D., & Fahle, M. (2013). Sight-reading in skilled pianists: Eye-hand span is independent of practice but associated with the musicians' cognitive abilities. 36th ECVP, Bremen (Germany).

Talks

(*) **Rosemann, S**., & Fahle, M. (2015). Dysfunctions of visual and auditory Gestalt perception (amusia) after stroke: Preliminary behavioral results. Neuroscientific Research Colloquium in the context of the German National Academic Foundation (Studienstiftung des Deutschen Volkes), Hamburg (Germany).

Rosemann, S., Altenmüller, E., & Fahle, M. (2015). The Influence of Practice, Expertise and Cognitive Skills on Sight Reading. Seminar "Imaging research methods in Music", University of Regensburg (Germany).

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Preface

Music is a special and unique part of human nature. Not only actively playing (making music in a group or alone) but also passive listening to music involves a richness of processes to make music the ideal tool to investigate how the human brain works.

Since childhood I have been interested in music and spent a great amount of my free time playing the guitar – as a soloist, in chamber music formations, and in a guitar orchestra. After advanced theoretical and pedagogic training I also gave my own guitar lessons until I started with my PhD. During my studies in neurosciences I was always interested in perceptual and cognitive deficits resulting from brain injuries caused by a stroke or neurological disorders.

This dissertation combines my professional interest in cognitive neurosciences with my non-academic interest in music and deals with the relationship between auditory, especially music, and visual dysfunctions after stroke. Behavioral investigations, lesion analysis, and functional magnetic resonance imaging were performed to assess the anatomical and functional correlates of these deficits.

A better and more detailed understanding of amusia and connected cognitive deficits is not only relevant in terms of fundamental neuroscience but also from a clinical point of view: symptoms of amusia are rare, mostly undiscovered, and the underlying mechanisms are hitherto insufficiently understood.

Abstract

Acquired amusia denotes the impaired perception of melodies, rhythms, and the associated disability to enjoy music which can occur after a stroke. Many amusia patients also show deficits in visual perception, language, memory, and attention. Hence, the question arises whether amusia actually describes an independent clinical picture or is better described by a general perceptual deficit for auditory, as well as visual, and speech-related material. Additionally, the question in what way impaired abilities in attention and working memory influence the performance in the music perception task remains to be investigated.

Within the scope of this dissertation, stroke patients were investigated with a series of behavioral tests at the stroke unit of the Klinikum Bremen Mitte. These tests included the examination of music perception, visual Gestalt perception, categorization, working memory abilities, attention, and of a few additional basic visual and auditory functions. Two amusic stroke patients were identified within a pool of twenty-five examined patients suffering small middle cerebral artery infarctions (full data only available for twenty patients). These amusia patients demonstrated selective deficits in music perception. Additionally, working memory and attention deficits were not related to impaired music perception. Lesion analysis showed involvement of small right-hemispheric areas within the basal ganglia in rhythm perception. We concluded that relatively pronounced lesions are able to damage a specific brain area engaged in a specific sub-function of music processing. Large lesions can lead to a wide variety of deficits, possibly because these lesions damage a large array of anatomically close but functionally distinct areas. Thus, the music perception network is composed of small and widely distributed areas which can be embedded in a brain region which is involved in other cognitive functions as well.

Furthermore, functional magnetic resonance imaging was used to investigate the influence of a stroke on the music perception network. For that aim, stroke patients and healthy control participants were measured during passive stimulation with a scene from German musical. The different conditions included unimodal auditory (only sound), unimodal visual (only vision) or bimodal visual-auditory (sound and vision as video presentation) sequences of the musical. For the analysis each condition was contrasted with a rest condition. Nine stroke patients and twenty-one control participants, nine of those were age- and gender-matched to the stroke patients, were measured. Comparison of stroke patients with healthy control participants showed compensation mechanisms in stroke patients recruiting additional brain regions for efficient perception of the stimuli. One amusic stroke patient demonstrated a very interesting pattern of BOLD activation for the

initial and re-test measurements. After six months the initially increased activation in frontal areas went back to normal and amusic symptoms were no longer found. Additional areas responsible for rhythm perception compensated for the initial damage of basal ganglia and the resulting deficit in rhythm perception. These were the supramarginal gyrus and inferior parietal lobule. Furthermore, insula activation was connected to amusia in general, possibly due to a strange and unpleasant perception of music.

Investigation of twenty elderly healthy participants showed an increased lateralization of the activation and high engagement of frontal areas in response to musical input. Highest contributions came from left lateralized activations in the precentral and inferior frontal gyri, postcentral gyrus and inferior parietal lobule, and superior temporal and transverse temporal gyri. Pre- and postcentral regions showed robust activation and seem to play a major role in processing our musical stimuli.

In sum, our results obtained from behavioral and functional magnetic resonance imaging measurements support the *modular view* of the music perception network. In this view a large array of brain regions in temporal, frontal, and parietal lobe are recruited to accomplish a certain sub-function of music. Additionally, damage to one of these modules leads to amusia symptoms, but reorganization processes may re-establish the concerned sub-function by compensatory mechanisms.

German Abstract/Deutsche Zusammenfassung

Eine erworbene Amusie ist eine durch eine Hirnschädigung verursachte Beeinträchtigung, Melodien und Rhythmen zu erkennen und der damit verbundene Verlust der Fähigkeit, Musik zu genießen. Viele der Patienten zeigen neben der Amusie auch Defizite in der visuellen Wahrnehmung, Sprache, Gedächtnis und Aufmerksamkeit. Es stellt sich daher die Frage, ob Amusie ein eigenständiges Krankheitsbild darstellt oder eher als eine generelle Wahrnehmungsstörung von sowohl auditivem, als auch visuellem und sprachlichem Material zu verstehen ist. Zudem ist bisher unklar, ob Defizite von Aufmerksamkeit und Gedächtnis die Bewältigung einer Aufgabe zur Musikwahrnehmung beeinflussen.

Im Rahmen dieser Doktorarbeit wurden Schlaganfall-Patienten auf der Schlaganfall-Station des Klinikums Bremen Mitte mit einer Reihe von Verhaltensuntersuchungen getestet. Diese Untersuchungen beinhalteten die Überprüfung von Musikwahrnehmung, visueller Gestaltwahrnehmung, Kategorisierung, Gedächtnisfunktionen, Aufmerksamkeitsleistung und einigen weiteren basalen visuellen und auditiven Funktionen. Von fünfundzwanzig Schlaganfall-Patienten mit kleinen Infarkten im Versorgungsgebiet der Arteria cerebri media wurden zwei Patienten als amusisch klassifiziert (komplette Daten für zwanzig Patienten vorhanden). Diese beiden Amusie-Patienten zeigten selektive Einschränkungen der Musikwahrnehmung. Zudem hingen Defizite in Arbeitsgedächtnis- und Aufmerksamkeitsleistungen nicht mit eingeschränkter Musikwahrnehmung zusammen. Die Läsionsanalyse zeigte, dass kleine rechtshemisphärische Areale in den Basalganglien mit der Rhythmuswahrnehmung assoziiert sind. Zusammenfassend konnten wir feststellen, dass relativ umschriebene Läsionen eine spezielle Hirnregion, die eine bestimmte Unterfunktion der Musikwahrnehmung ausführt, schädigen können. Größere Läsionen können eine Vielzahl an Defiziten hervorrufen, möglicherweise da größere Läsionen anatomisch benachbarte aber funktionell getrennte Areale schädigen. Folglich besteht das Netzwerk für Musikwahrnehmung aus kleinen weit verteilten Hirnarealen, die in größeren Hirnregionen mit anderen kognitiven Funktionen eingebunden sein können.

Des Weiteren wurden in dieser Doktorarbeit bildgebende Verfahren angewendet (funktionelle Magnetresonanztomographie), um den Einfluss eines Schlaganfalls auf das Netzwerk für Musikverarbeitung zu untersuchen. Hierzu wurden geeignete Schlaganfall-Patienten und gesunde Kontroll-Probanden mit einer passiven Stimulation durch ein kurzes Musical Video untersucht. Die Versuchsbedingungen beinhalteten unimodale auditive (nur Ton), unimodale visuelle (nur Bild) oder bimodale visuell-auditive (Ton und

Bild als Video) Sequenzen. In der Analyse wurden diese Versuchsbedingungen immer gegen eine Ruhebedingung kontrastiert. Neun Schlaganfall-Patienten und einundzwanzig gesunde Kontroll-Probanden, von denen neun alters- und geschlechts-angepasst waren, nahmen an diesen Untersuchungen teil. Der Vergleich der Schlaganfall-Patienten mit gesunden Kontroll-Probanden zeigte Kompensationsmechanismen der Schlaganfall-Patienten, die zusätzliche Gehirnareale für die effiziente Wahrnehmung der Stimuli rekrutierten. Ein Amusie-Patient zeigte ein sehr interessantes Aktivierungsmuster bei der initialen Messung und in der Nachuntersuchung. Die anfängliche erhöhte Aktivierung frontaler Areale sank nach sechs Monaten auf einen normalen Zustand und die Symptome der Amusie waren verschwunden. Zusätzliche Areale, die in der Rhythmuswahrnehmung involviert sind, kompensierten die initiale Schädigung der Basalganglien und die damit verbundene Störung der Rhythmuswahrnehmung. Diese Areale waren der supramarginale Gyrus und der inferiore parietale Lobulus. Außerdem war Aktivierung der Insula mit Amusie im Allgemeinen assoziiert, möglicherweise aufgrund der seltsamen und unangenehmen Wahrnehmung von Musik.

Die Untersuchung der zwanzig älteren gesunden Probanden zeigte eine erhöhte Lateralisierung der Aktivierung in frontalen Arealen in Bezug auf musikalische Stimulation. Links lateralisierte Aktivierungen in präzentralen und inferior frontalen Gyri, im postzentralen Gyrus und inferior parietalen Lobulus, und in den superior temporalen und transversen temporalen Gyri leisteten den größten Beitrag zur neuronalen Verarbeitung der Stimuli. Dabei zeigten prä- und postzentrale Gyri stabile Aktivierungen in allen Probanden; sie scheinen eine wichtige Rolle bei der musikalischen Verarbeitung zu spielen.

Zusammenfassend unterstützen unsere Ergebnisse aus Verhaltensuntersuchungen und funktioneller Magnetresonanztomographie die *modulare Sichtweise* des Netzwerks für Musikwahrnehmung. Laut dieser Sichtweise wird ein großes Netzwerk aus temporalen, frontalen und parietalen Arealen für bestimmte Sub-Funktionen in der Verarbeitung von Musik rekrutiert. Außerdem führt eine Schädigung eines dieser Module zu Symptomen einer Amusie, allerdings können Reorganisierungsprozesse die Ausführung der bestimmten Sub-Funktion als kompensatorische Mechanismen wiederherstellen.

Abbreviations

BOLD	Blood oxygenation level dependent
fMRI	Functional magnetic resonance imaging
IPL	Inferior parietal lobule
MBEA	Montreal Battery of Evaluation of amusia
TPJ	Temporoparietal junction
WM	Working memory

Theoretical Background

"The brain is by far our most fascinating and also complicated organ. They often say the brain is the most complicated piece of matter in the universe."

„Das Gehirn ist mit Abstand unser spannendstes Organ und auch unser kompliziertestes Organ. Man sagt ja oft, das Gehirn sei das komplizierteste Stück Materie, das es im Universum gibt."

Manfred Spitzer

1. Introduction

"The whole is entirely different from a mere sum. The nature of the whole determines what its parts are, and determines each part's place, role, and function within that whole."

(Wertheimer, 1923; Wertheimer, 2014)

Wertheimer's Gestalt theory describes how our sensory systems group together single elements of an object to 'a unified whole' (the Gestalt) in order to perceive the object correctly and efficiently. Important to note is that the whole is not merely more than the sum of the parts but that it is totally different from the sum of the parts (Wertheimer, 1923). Hence, the Gestalt determines what its parts must be and their attributes and relationships (Wertheimer, 2014). Imagine there are four equal straight lines and four right angles: if you group them together they can either become a square or a diamond, depending on how the different parts are arranged (their relationship to each other and to the viewer). The grouping occurs according to so-called Gestalt principles like proximity, similarity, continuity or common fate (parts that are close to each other, look similar, are aligned or move together are grouped together). Wertheimer's Gestalt theory is primarily known for its application in the visual domain, and most of the principles were formulated based on studies of visual perception, but they can be applied to any other modality as well. Already in 1890 van Ehrenfels described "Gestaltqualitäten" (Gestalt qualities) in terms of melody perception and recognition. Similarly, Wertheimer explored a Sri Lankan tribe (the Vedda) and used the term "Gestalt" when referring to structural features of their melodies (Wertheimer, 1910). Hence, the basis for the Gestalt theory lies in visual perception, but the term already originates in musicology (besides others of course).

When talking about auditory Gestalt perception in the context of this thesis we are considering the perception of music:

"A melody is the sum total of the notes composing it, plus the theme of the melody."

(von Ehrenfels, 1890; Wertheimer, 2014)

2. Auditory Gestalt Perception

2.1 Acquired Amusia – Clinical Picture

The ability to perceive, recognize and enjoy music can be affected by a stroke and as a result detection and recognition of melodies and rhythms are impaired, although primary auditory information processing is still intact (Griffiths, 1997). For the concerned patients

music sounds strange or even uncomfortable, they perceive 'disagreeable noise' and they do not enjoy listening to music anymore (DiPietro, Laganaro, Leemann, & Schnider, 2004; Griffiths, 1997; Mendez & Geehan, 1988; Quensel & Pfeifer, 1923). This dysfunction is termed acquired amusia (from now on simply amusia) and is widely reported in the literature (Ayotte, Peretz, Rousseau, Bard, & Bojanowski, 2000; DiPietro et al., 2004; Liegéois-Chauvel, Peretz, Babaï, Laguitton, & Chauvel, 1998; Mendez & Geehan, 1988; Quensel & Pfeifer, 1923; Steinke, Cuddy, & Jakobson, 2001; Tramo, Bharucha, & Musiek, 1990).

Analogously to visual agnosia (chapter 3.2) there are different types of amusia: *apperceptive amusia* is caused by a perceptual deficit (Stewart, von Kriegstein, Warren, & Griffiths, 2006). The long-term representation of music is still intact but patients cannot access it as already the analysis of music is impaired. Patients suffering apperceptive amusia e.g. cannot perceive a sequence of tones as a melody. A more infrequent type is the *associative amusia* which is characterized by a loss of music memory. Perceptual abilities are still preserved in this type of amusia but recognition processes are disturbed. As a result patients can perceive melodies as such and even discriminate between them, but they cannot identify their favorite music song. One can furthermore divide the apperceptive type of amusia into a *melodic* and a *temporal* dysfunction. A deficit in discriminating melodies can result from an impaired perception of melody (global aspect) or an impaired perception of pitch height (local aspect). Temporal dysfunctions are caused by deficits in discriminating rhythms. Case studies in the literature describe a double dissociation between melody (Griffiths, 1997; Peretz, 1990; Schuppert, Münte, Wieringa, & Altenmüler, 2000; Zatorre, 1985) and rhythm perception (DiPietro et al., 2004; Peretz, 1990; Schuppert et al., 2000; Vignolo, 2003).

Patients with a deficit in music perception often show deficits in visual-spatial abilities, executive functions, memory, learning, and attention as well (DiPietro et al., 2004; Griffiths, 1997; Särkämö et al., 2009a; Särkämö et al., 2009b). Language impairments often also accompany amusic symptoms (DiPietro et al., 2004; Eustache, Lechevalier, Viader, & Lambert, 1990; Patel, Peretz, Tramo, & Labreque, 1998) and one study revealed that all stroke patients suffering from visual neglect also showed amusia symptoms (Särkämö et al., 2009a). Considering all these findings in context, the question arises whether the visual and cognitive deficits represent an epiphenomenon of amusia (or rather vice versa) or whether the clinical picture of amusia actually depicts a general deficit in perceiving (auditory and visual) 'Gestalts'.

The challenge to compare studies about amusia cases lies in the fact that the studies differ in terms of 1) the recruitment of patients (single case versus group studies; symptom-based versus lesion-based) as well as 2) the localization of the lesions (unilateral versus bilateral). Moreover standardized methods to test music perception were missing (Zatorre, 1985). Only in 2003 a battery for testing music perception was invented which is globally used now (Montreal Battery of Evaluation of Amusia; Peretz, Champod, & Hyde).

2.2 Neuronal Correlates of Amusia

The versatile clinical picture of amusia and the accompanied cognitive dysfunctions result from the fact that processing music is based on a distributed neuronal network with specialized subsystems (Alossa & Castelli, 2009; Peretz & Coltheart, 2003). Previous investigations indicate only few suggestions about the neuroanatomical correlates of amusia (detailed review: Stewart et al., 2006). Typical lesion locations which are reported to induce amusia symptoms are mainly found in the superior and middle temporal gyrus (Ayotte et al., 2000; DiPietro et al., 2004; Eustache et al., 1990; Griffiths, 1997; Liegéois-Chauvel et al., 1998; Mendez & Geehan, 1988; Patel et al., 1998; Peretz et al., 1994; Piccirilli, Sciarma, & Luzzi, 2000; Satoh et al., 2005) but other brain areas like the insula (Ayotte et al., 2000; Griffiths, 1997; Hochman & Abrams, 2014; Patel et al., 1998), the inferior parietal lobule (DiPietro et al., 2004; Patel et al., 1998), and frontal areas (Botez & Wertheim, 1959; Eustache et al., 1990; Johkura, Matsumoto, Hasegawa, & Kuroiwa, 1998; Patel et al., 1998; Steinke et al., 2001) are also mentioned. Often, these patients do not suffer from pure amusic symptoms but from generalized auditory agnosia characterized by deficits in recognizing and differentiating between non-verbal and verbal sounds. Therefore no firm conclusions about neuro-anatomical correlates of amusia can be drawn, except that music is processed in different modules of the brain and these processes are not lateralized (Alossa & Castelli, 2009).

Further findings of case-studies with acquired amusia patients and neurological patients with similar dysfunctions led to the development of a model for music processing (Alossa & Castelli, 2009; García-Casares, Berthier Torres, Froudist Walsh, & González-Santos, 2013; Peretz & Coltheart, 2003; Figure 2.1). It is divided into a temporal and a pitch organization module additionally to various other components connected with music perception (e.g. emotion, lexicon). These two processing streams work in parallel and largely independent. The temporal modules deal with rhythm (temporal grouping) and meter (temporal beat) of the stimulus. The pitch modules are concerned with pitch height, scale, intervals, and contours of melodies. Both melodic and rhythmic modules project to the components for emotion expression and musical lexicon. The emotion expression

module enables the listener to recognize and experience the emotion which is expressed in the music. On the other hand the musical lexicon contains representations of musical phrases collected during lifetime and serves to recognize familiar tunes. In combination with associative memories one can retrieve nonmusical information, e.g. the name of the tune. Processing components (shown as boxes) or the flow of information between different components (arrows between boxes) could be damaged as indicated in patients with dissociative deficits. Furthermore, the model can be applied to any acoustic input, not only music, and hence it accounts for any auditory 'Gestalt'.

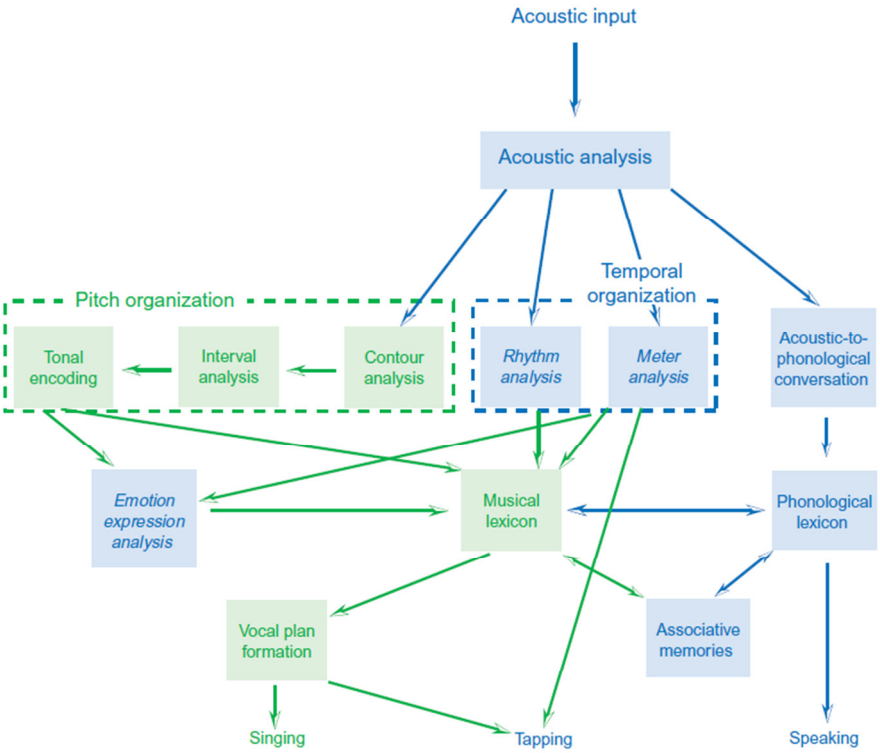

Figure 2.1: Model of music processing developed by Peretz & Coltheart (2003).

Hemispheric lateralization has also been addressed in the model: it was suggested that the right hemisphere processes melodic information and that rhythm is processed in both hemispheres (Alossa & Castelli, 2008; García-Casares et al., 2013; Stewart et al., 2006). Johnsrude, Penhune, & Zatorre (2000) found that patients with right (but not left) temporal lobe removal overlapping with the Heschl's gyrus showed significantly higher thresholds in judging direction of pitch changes but not in pitch discrimination. These patients showed selective deficits in using pitch contour information suggesting that subtle functional specializations of specific sub-regions within the music perception network exist.

Functional correlates of acquired amusia were not investigated so far but there are a lot of magnetic resonance imaging (fMRI) studies about music processing in healthy subjects (Gaab, Gaser, Zaehle, Jäncke, & Schlaug, 2003; Jerde, Childs, Handy, Nagode & Pardo, 2011; Koelsch et al., 2002; Koelsch, Fritz, Schulze, Alsop, & Schlaug, 2005; Lee, Janata, Frost, Hanke, & Granger, 2011; Norman-Haignere, Kanwisher, & McDermott, 2013; Patterson, Uppenkamp, Johnsrude, & Griffiths, 2002; Platel et al., 1997; Rogalsky, Rong, Saberi, & Hickok, 2011; Stewart, Overath, Warren, Foxton, & Griffiths, 2008).

2.3 Neuronal Basis of Music Perception

Based on results from fMRI studies with healthy participants the model of music processing has been revised and new findings have been added (Koelsch, 2011; Schuppert et al., 2000; Stewart et al., 2006). All modules described here (as in the other model as well) can be applied not only to music but also to other acoustic material, e.g. speech, as similar features are shared and processed (Figure 2.2). First, acoustic information is decoded and transformed in the auditory brainstem, the superior olivary nucleus and the inferior colliculus (Feature extraction I). These structures show responses to periodicity of sounds, timber, roughness, and sound intensity (Koelsch, 2011). Then features of the tones have to be extracted (e.g. pitch height, timbre, intensity) which is accomplished by primary and secondary auditory cortices (Feature extraction II). The primary and secondary auditory cortices are located in the medial part of the Heschl's gyrus, which can be found in the superior temporal cortex. Pitch is needed to construct melodies, chords, and harmonies which are the next steps of analysis. The process of Gestalt creation involves melody and rhythm formation as well as timbral and spatial grouping with the help of Gestalt principles such as similarity, proximity, and continuity (Gestalt formation; Koelsch, 2011; Wertheimer, 1923). Gestalt formation is supposed to take place in the planum temporale which lies posterior to Heschl's gyrus. Analysis of chords, contour, and time intervals belong to the process of Gestalt formation (Analysis of intervals). Cognitive analysis of sequential tones refers to melody and harmony construction and is processed by a network situated in the frontal lobe including premotor cortex, dorsolateral prefrontal cortex, and the inferior frontal gyrus (Structure building). Temporal processing in terms of rhythm or meter activates a network of superior-temporal cortices, the cerebellum, and basal ganglia (Structure building).

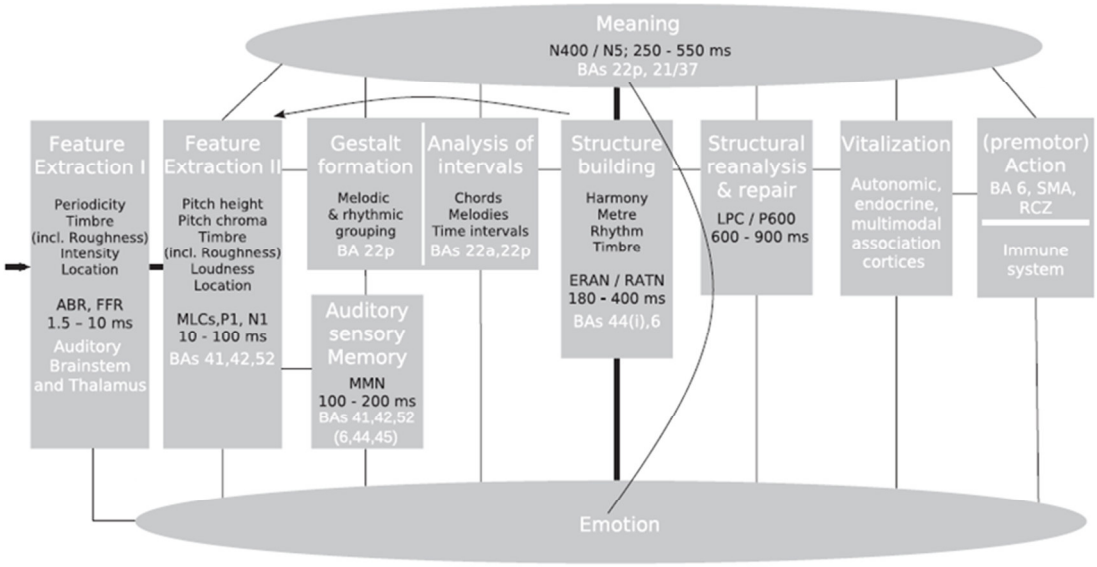

Figure 2.2: Neuro-cognitive model of music processing developed by Koelsch (2011).

Other studies have found that not only areas in inferior frontal cortices but also temporal areas (bilaterally) are involved in musical structure building (Fedorenko, McDermott, Norman-Haignere, & Kanwisher, 2012). Furthermore, both premotor and supplementary motor areas, as well as basal ganglia, play important roles in beat perception (Fedorenko et al., 2012; Grahn & Brett, 2009; Zatorre, Chen, & Penhune, 2007). These findings are supported by other patient groups: Parkinson and stroke patients with damage in the basal ganglia have difficulty detecting beat or rhythm-based differences in melodies (Grahn & Brett, 2009; Merchant, Luciana, Hooper, Majestic, & Tuite, 2008; Schwartze, Keller, Patel, & Kotz, 2011). Further studies showed that parietal areas like intraparietal sulcus and inferior parietal lobule are activated during pitch and contour processing (Foster & Zatorre, 2009; Lee et al., 2011; Schwenzer & Mathiak, 2011). Attentive listening to music is achieved by frontal, temporal, and parietal areas, brain regions usually involved in domain-general attention and working memory (WM) functions (Janata, Tillmann, & Bharucha, 2002). Rhythm perception recruits several brain regions in frontal, parietal, and temporal cortices as well (Thaut, Trimarchi, & Parsons, 2014).

Comparing typical lesions in amusia patients with the model evaluated on the basis of healthy music processing one can see that many individual patients do not fit the preliminary model. Recently, an updated neuroanatomical framework based on amusia patients and fMRI studies in healthy participants has been proposed (Figure 2.3; Clark, Golden & Warren, 2015). It shows a network consisting of regions processing relatively selective components of music, with extensive overlap with brain areas processing language or other complex auditory material. This network is highly complex and widely distributed over temporal, frontal, and parietal lobes, additional to subcortical and limbic

structures. It mostly overlaps with previous models (Peretz & Coltheart, 2003; Koelsch, 2011), but enables a further distinction between selective types of amusia (not only differentiated between associative and apperceptive).

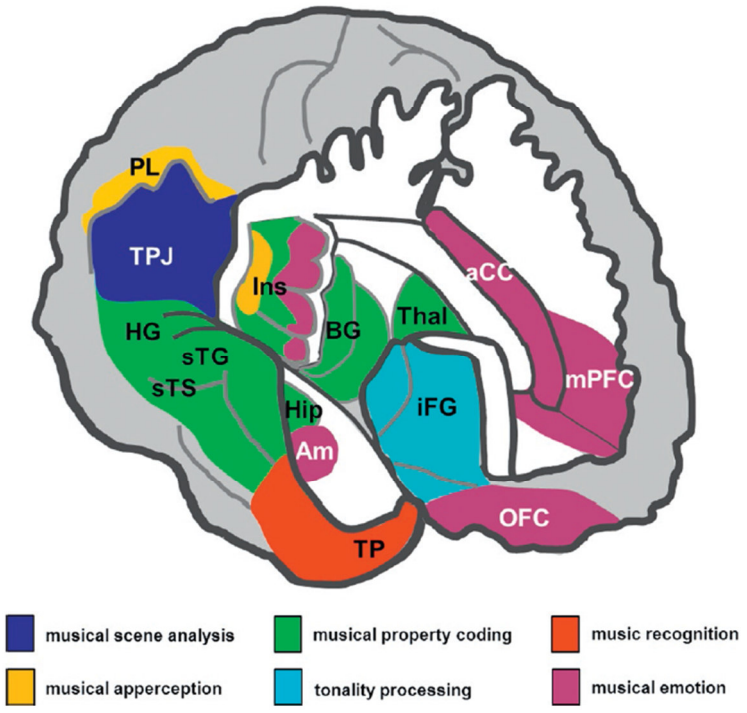

Figure 2.3: Model of neuroanatomy of music processing developed by Clark, Golden, & Warren (2015). The figure depicts the right hemisphere with partly removed cortical envelope to expose deep brain structures (although important structures are equally distributed in both hemispheres). Colours indicate brain damage shown to impair the specific process. Abbreviations: aCC, anterior cingulate cortex; Am, amygdala; BG, basal ganglia; HG, Heschl's gyrus; Hip, hippocampus; iFG, inferior frontal gyrus; Ins, insula; mPFC, medial prefrontal cortex; OFC, orbitofrontal cortex; PL, parietal lobe; sTG, superior temporal gyrus; sTS, superior temporal sulcus; Thal, thalamus; TP, temporal pole; TPJ, temporoparietal junction.

Taken together, the model for music processing in healthy participants shows that the right hemisphere seems to process melodic information (mainly superior temporal and frontal areas) while both hemispheres are responsible for rhythm perception (mainly superior temporal areas, cerebellum, and basal ganglia) (Clark, Golden, & Warren, 2015; García-Casares et al., 2013; Stewart et al., 2006). Despite several suggestions for a provisional model of music processing, any model can only be preliminary and any new patient with specific deficits will add knowledge to it. Hence, work with amusia patients seems to be an essential key to find a consensus about the music processing network.

3. Visual Gestalt Perception

3.1 Visual Processing

In the visual domain we can also perceive 'Gestalts' by grouping single elements of an object with the help of the so-called Gestalt principles like good continuation or proximity (Wertheimer, 1923; Westheimer, 1999).

Gabor arrays are often used as stimuli for the assessment of visual Gestalt perception (Figure 3.1): these are composed of a number of Gabor elements (either random or same orientation) and a target Gabor shape to be detected by aligned elements (principle of good continuation, Wertheimer, 1923). If the Gabor elements making up the target are not aligned, the detection ability is reduced (Field, Hayes, & Hess, 1993). Behavioral studies showed that the detection of a target Gabor shape is enhanced when interior elements have the same orientation compared to exterior elements (Machilsen & Wagemans, 2011), but that there is no effect if all interior and exterior elements are aligned or else random (Sassi, Machilsen, & Wagemans, 2012). Furthermore, it was revealed that closure and smoothness of the presented targets increases the detectability (Kovács & Julesz, 1993; Mathes & Fahle, 2007).

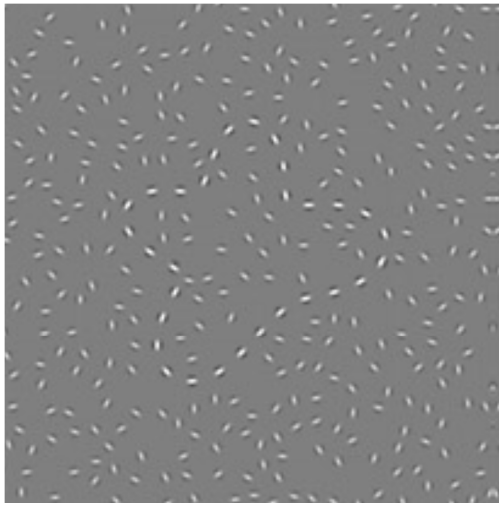

Figure 3.1: An example of a Gabor array used by Machilsen & Wagemans (2011).

Early studies dealing with visual processing suggested that there is a division of early versus late processing which involves different processing steps and corresponding brain areas (Felleman & Van Essen, 1991). Local features like orientation, color, contrast and shape were supposed to be processed by early visual areas (striate and extrastriate areas) while recognition of an object was thought to take place in higher visual areas (inferior temporal and posterior parietal cortices). These higher visual areas can be divided into

two streams: the dorsal (occipito-parietal) stream for object recognition and the ventral (occipito-temporal) stream for motion and spatial information processing (Barton, 2011). Later functional magnetic resonance imaging (Altman, Bülthoff, & Kourtzi, 2003; Dumoulin & Hess, 2006; Kourtzi & Huberle, 2005; Kourtzi, Tolias, Altmann, Augath, & Logothetis, 2003; Malach et al., 1995) and electroencephalographic studies (Herrmann & Bosch, 2001; Machilsen, Novitskiy, Vancleef, & Wagemans, 2011; Volberg & Greenlee, 2014) found that both early and higher visual areas are associated with the process of Gestalt perception: it was demonstrated that early visual areas were correlated with processing of *local* information (e.g. orientation and contour of Gabor elements) while higher visual areas showed responses to perception of the *global* information (shape of the contour) of the stimuli. Besides parieto-occipital and occipito-temporal areas of the brain, the temporoparietal junction (TPJ) is thought to play a major role in global Gestalt perception (Huberle & Karnath, 2012). A bilateral representation of Gestalt perception in the TPJ has been proposed, but different clusters within the TPJ were found to be involved (Renning, Bilalić, Huberle, Karnath, & Himmelbach, 2013; Ritzinger, Huberle, & Karnath, 2012). In a recent study the role of the right anterior TPJ in processing novel global forms has been identified (Renning, Himmelbach, Huberle, & Karnath, 2015). In contrast, another study using perceptual alternations between the perception of local dot motion and global illusionary square motion found reduced beta-band power in the posterior parietal cortex during the perceptual grouping phase (Zaretskaya & Bartels, 2015). Hence, an exact localization of where 'Gestalts' are formed in the human brain remains unresolved.

Some of the current findings concerning neuronal correlates of visual Gestalt perception result from and are supported by cases of patients suffering from visual agnosia.

3.2 Visual Agnosia

The term visual agnosia refers to impairments in visual object perception despite intact visual fields and basic visual functions (e.g. orientation, luminance, contrast, color perception). These can be present after occipito-temporal brain injury (De Renzi, 2000). Similar to amusia one can differentiate between an apperceptive and an associative type of agnosia: *apperceptive* agnosias affect the sensory perception and the *associative* term is used to describe a disorder in the recognition process. In the former case the object cannot be reconstructed whereas in the latter case the object can be perceived but the meaning of it cannot be accessed. Distinction between both types can be made by the help of a copying task: patients suffering the apperceptive agnosia type cannot copy a presented object but

associative agnosic patients mostly succeed in the copying task. For both types the recognition of the object can be achieved based on haptic or auditory information.

We can further classify different forms of agnosia: *visual form agnosia* (de-Wit, Kubilius, Op de Beek, & Wagemans, 2013; Grossman, Galetta, & D'Esposito, 1997; Karnath, Rüter, Mandler, & Himmelbach, 2009) and *integrative visual agnosia* (Riddoch & Humphreys, 1987). As a result patients show deficits in discriminating between shapes as well as to recognize objects (*form agnosia*) or they demonstrate deficits in integrating local aspects into global shapes (*integrative agnosia*). The latter patients may be able to copy simple designs but they are not able to perceive the whole object.

Simultanagnosia is another – differentiated – form of agnosia (Himmelbach, Erb, Klockgether, Moskau, & Karnath, 2009; Huberle & Karnath, 2006; Luria, 1959; Wolpert, 1924). These patients have difficulties in detecting global shapes (several elements at the same time) with preserved ability to recognize single elements of the whole shape. The deficit of simultanagnosia is associated with lesions in the occipitoparietal cortex – an area responsible for integrating multiple elements into a unified perception of the whole object (Himmelbach et al., 2009). Perceptual grouping impairments were shown for all of these cases.

Shape perception deficits were also found in the intact hemifield of hemianopic patients (Cavézian et al., 2010; Paramei & Sabel, 2008; Schadow, Naue, Herrmann, Sabel, & Paramei, 2006; Schadow et al., 2009) assessed by psychophysics and electrophysiological measurements. These studies suggest that the stroke damages higher visual areas responsible for Gestalt perception and interhemispheric projections leading to perceptual deficits in the ipsilesional hemifields.

Patient DF was intensively studied as she presented a visual form agnosia due to carbon monoxide intoxication (Carey, Harvey, & Milner, 1996; de-Wit et al., 2013; Goodale, Milner, Jakobson, & Carey, 1991; Goodale et al., 1994; Milner et al., 1991; Whitwell, Milner, Cavina-Pratesi, Barat, & Goodale, 2014). She was unable to discriminate simple geometric shapes and objects but guidance of hand and finger movements in interaction with objects was accurate. It was shown that she did not benefit from Gestalt grouping principles like similarity or proximity, but recognition of 'parts' was preserved. These dysfunctions resulted from lesions in the lateral occipital cortex (the 'ventral stream' in visual processing) (James, Culham, Humphrey, Milner, & Goodale, 2003) and demonstrated that the perception of the "Gestalt" is not achieved without higher visual processing (de-Wit et al., 2013).

There are also specific forms of *associative* agnosia (where the meaning of an object cannot be accessed). The disorder can affect different 'categories' like faces or animated objects depending on which area of the brain is damaged (see chapter 4.1).

4. Categorization

Grouping is also required for higher visual and auditory functions where meaning and relevance meet perception. One of such processes is categorization. The process of categorization includes the classification of an object to a category containing equivalent objects, different from objects of another category. In order to correctly categorize an object we have to recognize and compare it with stored representations (Rosch, Mervis, Gray, Johnson, & Boyes-Braem, 1976) which is closely related to Gestalt formation and object detection (for a review see Mack & Palmeri, 2011; Grill-Spector & Kanwisher, 2005; Riesenhuber & Poggio, 1999).

4.1 Visual Categorization

Although the underlying mechanisms of categorization are yet not fully understood, there is a consensus about the bidirectional communication of early and higher cortical areas in which bottom-up information is exchanged with top-down knowledge (Bar et al., 2006; Davenport & Potter, 2004; Evans & Treisman, 2005; Fabre-Thorpe, Delorme, Marlot, & Thorpe, 2011; Frith & Dolan, 1997). Categorization can be achieved at very short presentation latencies (usually around 50 ms) (Delorme, Richard, & Fabre-Thorpe, 2010; Delorme, Rousselet, Macé, & Fabre-Thorpe, 2004; Fabre-Thorpe et al., 2011; Joubert, Fize, Rousselet, & Fabre-Thorpe, 2008; Rousselet, Macé, & Fabre-Thorpe, 2003; Serre, Oliva, & Poggio, 2007; Thorpe, Fize, & Marlot, 1996; VanRullen & Thorpe, 2001). Response times in this paradigm are short (250 ms after stimulus presentation) as well, hence this is called ultra-rapid categorization. It is the result of purely feed-forward information processing, but as stimuli get more complex, top-down information is needed to accomplish the task (Fenske, Aminoff, Gronau, & Bar, 2006; Serre, Oliva, & Poggio, 2007).

Object categorization can be achieved according to three levels of abstraction first defined by Rosch and colleagues (1976): the intermediate or basic level (dog vs. cat), the superordinate level (animal vs. car), and the subordinate level (Saint Bernard vs. German shepherd). Thus, one and the same object can be categorized as an animal, a dog or a Saint Bernard – depending on the task. The level at which categorization is fastest is called the entry-level. At the basic level the categorization process seems to be fastest for most

objects possibly because this process occurs prior to super- and subordinate categorization and therefore seems to be a prerequisite for further processing (termed basic-level-advantage) (Rogers & Patterson, 2007; Rosch et al., 1976). Additionally it seems to be the most natural way to categorize objects: objects in the same category share many features while objects in different categories share few features. In contrast objects of different subordinate categories also share many features (Saint Bernards and German shepherds both have fur, four legs, snout, and other features common in dogs). Hence, the basic level is the most inclusive level at which objects look similar (Tanaka & Taylor, 1991).

But the basic level is not always the entry level: Joliceur and colleagues (1984) found an advantage of subordinate levels for atypical members of a category, e.g. one would first categorize a penguin as a penguin and not as a bird whereas a robin would be first categorized as a bird and then as a robin. Furthermore, experts can also categorize objects at the subordinate level as fast and accurate as objects at the basic level – known as the entry-level shift (for a review see Mack & Palmeri, 2011; Rosch et al., 1976; Tanaka & Taylor, 1991). Still all of these studies support the idea of a two-stage process in categorization with first access of the basic level and then the processing of super- and subordinate features (Jolicoeur, Gluck, & Kosslyn, 1984; Rosch et al., 1976). Another theory emerged as the basic level advantage was further challenged by some recent studies (Macé, Joubert, Nespoulous, & Fabre-Thorpe, 2009; Prass, Grimsen, König, & Fahle, 2013): for ultra-rapid categorization significant faster reaction times and higher accuracies for the superordinate level than for the basic level were shown. Thus, the second theory proposes a parallel-processing model where first superordinate and then basic and subordinate levels are accessed like broad to fine tuning (Macé et al., 2009; McClelland & Rogers, 2003; Prass et al., 2013; Rogers & Patterson, 2007). In this model the basic level advantage arises because of similarity-based generalizations, e.g. when we learn that a robin is a bird, we generalize the name bird to other types of birds.

Not only different levels of abstraction and expertise have an effect on the speed and accuracy of categorization, but also the category itself (e.g. animate versus inanimate objects) and the context of the stimuli (different backgrounds) may influence categorization performance. The category effect is still a controversial issue. Distinct brain areas for the processing of animate versus inanimate stimuli (Chao, Weisberg, & Martin, 2002; Gerlach, 2007; Mahon, Anzellotti, Schwarzbach, Zampini, & Caramazza, 2009; Martin, 2007) and for special stimuli like faces, words, and numbers (Allison, McCarthy, Nobre, Puce, & Belger, 1994; Kanwisher, McDermott, & Chun, 1997) have been shown in healthy participants. Hence, regions like the fusiform face area (Kanwisher et al., 1997),

parahippocampal place area (Epstein & Kanwisher, 1998) and visual word form area (Nobre, Allison, & McCarthy, 1994) were identified. Selective impairments for either category were reported in patients (*associative agnosia*) (Capitani, Laiacona, Mahon, & Caramazza, 2003; Caramazza & Mahon, 2003; Hillis & Caramazza, 1991; Humphreys & Forde, 2001; Warrington & Shallice, 1984). In behavioral studies some do not find differences across categories (VanRullen & Thorpe, 2001), others find an advantage for animate objects (Crouzet, Joubert, Thorpe, & Fabre-Thorpe, 2012; Hillis & Carmazza, 1991; McMullen & Purdy, 2006), yet others for inanimate objects (Hillis & Carmazza, 1991; Warrington & Shallice, 1984). Even within one study with different categorization levels advantages for either category were shown (Prass et al., 2013).

The same holds true for context effects: inversion (Rousselet et al., 2003) and semantic inconsistency seem to decrease performance (Davenport & Potter, 2004; Joubert et al., 2008), presentation of isolated objects on gray background increased performance and speeded up response times in some studies (Davenport & Potter, 2004; Prass et al., 2013) but was shown to have no effect in another study (Joubert et al., 2008).

4.2 Auditory Categorization

In the auditory domain categorization of sounds is based on certain acoustic features and hence enables an efficient and appropriate response of the listener (Tsunada & Cohen, 2014). These features can belong to different types of input: sounds, tones, and speech. Within these different areas, more 'abstract' types of categories can be formed: some stimuli are grouped together as a category based on several shared features – equivalent to different levels of abstraction in the visual domain (Rosch et al., 1976; Russ, Lee, & Cohen, 2007).

These different semantic representations are processed by distinct cortical networks in the human brain: human sounds – including speech – recruit posterior superior temporal sulci, fronto-parietal regions, insula, and sub-cortical regions while animal sounds are processed in the superior temporal gyrus, and the insula (Belin, Zatorre, Lafaille, Ahad, & Pike, 2000; Desai, Liebenthal, Waldron, & Binder, 2008; Engel, Frum, Puce, Walker, & Lewis, 2009; Lewis, Brefczynski, Phinney, Janik, & DeYoe, 2005; Lim, Fiez, & Holt, 2014). Mechanical and tool sounds show increased blood oxygenation level-dependent (BOLD) signals in anterior superior temporal gyri, parahippocampal regions but also in distinct parietal and frontal regions while environmental sounds activate dorsal occipital and medial parietal cortices (Engel et al., 2009; Lewis et al., 2005). A further distinction can be made for action- versus non-action-related sounds (Pizzamiglio et al., 2005): action-

related sounds are correlated with activation in temporal and premotor areas while the temporal role is involved with processing non-action-related sounds. Another study found that within the auditory cortex the anterior superior temporal regions show category-selective responses (to musical instrument sounds and human speech) whereas activation in regions closer to primary auditory cortex correlated with specific acoustic features of natural sounds (e.g. temporal modulation), and therefore supports a hierarchical organization of the anteroventral auditory processing stream (Leaver & Rauschecker, 2010). Studies with patients suffering from *auditory agnosia* (deficits in discriminating or recognizing different types of sounds) show that lesions to the TPJ induce deficits in parsing (analysis of the sentences) and damage to the more anterior temporal lobe lead to deficits in sound recognition (Goll, Crutch, & Warren, 2012).

The temporal and prefrontal cortices are highly interconnected and important areas for auditory category formation and retrieval (Freedman, Riesenhuber, Poggio, & Miller, 2001; Russ et al., 2007; Tsunada & Cohen, 2014). Moreover, both areas are also involved in processing visual category information, hence again reflecting processes of association, memorizing and learning rules (Freedman et al., 2001; Freedman, Riesenhuber, Poggio, & Miller, 2002; Freedman, Riesenhuber, Poggio, & Miller, 2003; Russ et al., 2007). Temporal areas seem to be more associated with physical properties, while the prefrontal areas are more involved with processing category memberships, associations, meaning and memory. A study exploring both visual and auditory categorization showed that the inferior frontal gyrus seems to be an important region related to both auditory and visual object semantic material (Adams & Janata, 2002). Additionally the middle temporal gyrus seems to integrate information from auditory and visual modalities (Beauchamp, Lee, Argall, & Martin, 2004).

There is evidence that visual and auditory material is similarly perceived across both categories. Primary visual and auditory areas are more associated with processing physical properties of the stimuli while frontal areas are linked to category formation, association and retrieval of information.

5. Objective of the Thesis

5.1 Thematical Motivation

Patients with focal brain lesions suffering from specific behavioral deficits tell us a lot about the brain. From these patients we are able to draw conclusions about functions of specific brain areas. Just to mention a few examples from history, research of brain-damaged patients enabled to identify regions involved in language processing (Broca's and Wernicke's area), specialized visual processing (fusiform face area, parahippocampal place area) or memory formation (Patient HM and his removal of the hippocampus). In the context of music perception investigations of stroke patients showed that music processing is not lateralized (like language) and that there is a double dissociation between melody and rhythm perception.

Furthermore, we know that brain damage does not only affect the focal area that is injured but has widespread implications for other brain areas as well (Calautti, Leroy, Guincestre, Mariè, & Baron, 2001a; Feydy et al., 2002; Gratton, Nomura, Pèrez, & D'Esposito, 2012; Grefkes et al., 2007; Karnath et al., 2005; Marshall et al., 2000; Meehan, Randhawa, Wessel, & Boyd, 2011; Ward, Brown, Thompson, & Frackowiak, 2003). Often these brain areas are connected and belong to a whole network of regions accomplishing a specific function. Hence, not only damage to one specific area impairs the correct execution of that function (but damage to one of several possible areas could do that) and the damage could lead to dysfunctions of other connected areas too.

Amusia patients often also show other perceptual and cognitive deficits. These can affect visual-spatial abilities, executive functions, memory, learning, attention, and language skills (DiPietro et al., 2004; Eustache et al., 1990; Griffiths, 1997; Patel et al., 1998; Särkämö et al., 2009a; Särkämö et al., 2009b). It was also revealed that stroke patients suffering from visual neglect were impaired in music perception (Särkämö et al., 2009a).

When considering findings from clinical studies and from imaging experiments in healthy subjects, one can notice that brain areas supposed to induce amusia symptoms and brain areas demonstrated to be involved in healthy music processing do not always match (García-Casares et al., 2013; Koelsch, 2011; Stewart et al., 2006).

Taken together, the following assumptions can be ascertained so far: 1) Music perception is accomplished by a widely distributed network; 2) Amusia symptoms can arise if this network is damaged by e.g. a stroke; 3) Often amusia symptoms are accompanied by other perceptual and cognitive deficits; 4) A stroke can have widespread implications on other

brain areas; 5) The models for music processing and lesions resulting in amusia are not consistent across the literature. Considering all these findings from past research it seems to be convenient to study brain lesions and music perception in combination. The objective of this dissertation is to investigate widespread effects of a stroke on other areas and functions of the brain. More specifically the aim is twofold: a) on one hand behavioral measurements should be conducted in order to address the question whether visual and cognitive deficits coming along with amusia represent an epiphenomenon or whether amusia actually is better described by a general deficit in perceiving 'Gestalts' (Manuscript "Musical, visual and cognitive deficits after middle cerebral artery infarction", chapter 6); b) on the other hand imaging tools like fMRI come into play to investigates changes in brain activation in brain areas belonging to the music perception network after a stroke (Manuscript "Amusia after stroke – an fMRI study", chapter 7). Additionally, the music perception network was explored in twenty healthy elderly people to identify effects of aging which may complicate the view about music perception in healthy young individuals and usually elderly stroke patients with amusia (Manuscript "Lateralization of music perception in healthy elderly people – an fMRI study", chapter 8). A summary of the current findings and the arising questions can be seen in figure 5.1.

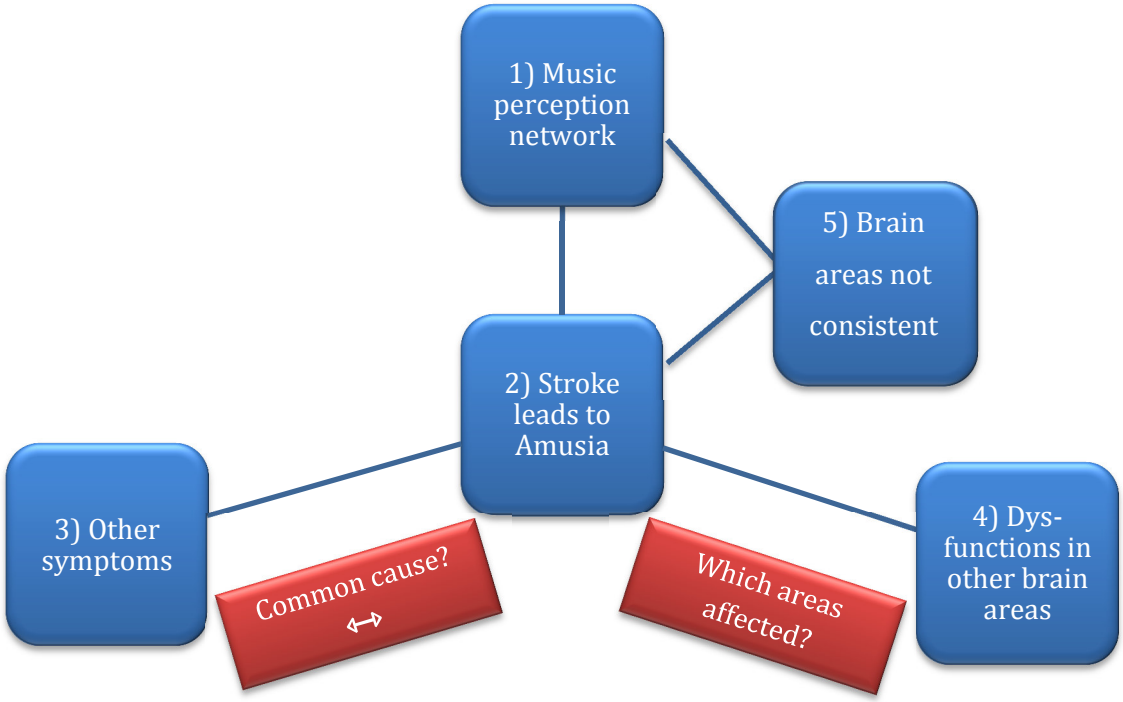

Figure 5.1: Assumptions and arising questions for the present thesis.

5.2 Operationalization

In order to address the objective of the present thesis, two different methods have been applied: a) behavioral measurements and b) functional magnetic resonance imaging. All experiments are described in detail in the 'Manuscripts'-section. However, the scientific considerations for the design of both measurements are presented below.

5.2.1 Behavioral Measurements

The key element of the behavioral measurement is the Montreal Battery of Evaluation of amusia (MBEA; Peretz, Champod, & Hyde, 2003). The MBEA is a globally used battery and consists of six subtests. Särkämö and colleagues (2009) showed that the subtests 'scale' assessing melody perception and 'rhythm' assessing rhythmic perception are sufficient to adequately assess music perception skills. Therefore only these two subtests are administered in the experiments described in this dissertation. These two different tests are needed because of the double dissociation between melody and rhythm perception. In both tests the participants hear two melodies and have to decide whether or not they are the identical. In fifty percent the melodies are the same, in fifty percent they are not: in the scale task, the melody is changed by one tone which is out of scale; in the rhythm task, the temporal order of two succeeding tones is altered.

Having a closer look at the MBEA, there are several possible conclusions one can come to, if a patient is scoring bad in the test: a) the patient is suffering amusia; b) the patient has general attention deficits; c) the patients has WM impairments; d) the patient has a more widespread deficit in the perception of auditory and maybe also visual material. Besides these, first of all it is necessary to confirm that this deficit does not result from peripheral hearing loss, established via audiometric testing. Additionally, a lot of other tests will be conducted in the behavioral measurement to assess visual, language, attention, and WM functions of the participants. The core of these tests is formed by a visual Gestalt perception test and a categorization task self-designed for four different modalities (auditory, visual, nonverbal and verbal). With the help of these the aim was to systematically check whether amusic symptoms are music specific, auditory specific (also affecting language), specific for nonverbal material (also visually presented) or result from a general deficit in the perception of Gestalts. This general deficit would be characterized by impaired visual and auditory perception of simple geometric figures and music input, as well as categorization deficits. The visual Gestalt perception test is a mixture of already established material in state-of-the-art visual Gestalt perception tasks (chapter 3.1) and the participants' task in the MBEA. Two Gabor arrays with a Gestalt formed by aligned Gabors are presented and participants have to decide whether or not the seen Gestalts

were identical. Hence, both the MBEA and the visual Gestalt task seem to be comparable across modalities. In the categorization task, participants have to decide whether the presented stimulus is an 'animal' or a 'means of transportation'. Stimuli are presented on grey background. This task is widely used in the literature and the grey background is supposed to facilitate the categorization process (Prass et al., 2013).

Besides a better and more detailed understanding of amusia and the connected perceptual and cognitive deficits, findings of the connection between the different functions and impairments could also be helpful and important for rehabilitation matters. Regeneration of a specific ability may improve music perception, or vice versa (Ripollés et al., 2015; Särkämö et al., 2008; Särkämö et al., 2009; Särkämö et al., 2010; Särkämö et al., 2014).

5.2.2 Functional Magnetic Resonance Imaging

As a second step functional magnetic resonance imaging (fMRI) was applied. With this method the (BOLD) signal of different brain regions in response to different stimulations can be determined. As no fMRI experiment was done with patients suffering from acquired amusia so far, this step was taken within the scope of the present dissertation.

The stimulation paradigm consisted of four different conditions: unimodal auditory, unimodal visual, bimodal (auditory and visual) synchronous and bimodal asynchronous stimulation. A block design with rest condition alternating with stimulation sequences consisting of a German Musical song was used. The aim was to investigate in which areas an abnormal (increased or decreased) BOLD signal can be found in amusia patients compared to other stroke patients and healthy controls. Additionally, it should be explored whether these areas (with abnormal signal) not only respond to the unimodal but also to the bimodal modality. The asynchronous bimodal condition was designed to check whether or not amusia patients show a less pronounced BOLD signal to this condition compared to the synchronous condition, maybe induced by altered perception of the music presented in the stimulation sequence. The idea was that if the perception of music was disturbed anyway (sounding strange or uncomfortable), the asynchronous presentation should not induce a great difference compared to synchronous presentation as we would expect in participants with normal music perception.

However, the BOLD signal in post-stroke patients must be interpreted with caution. The BOLD signal is an indirect measure for brain function and it is highly dependent on the relationship between increase of local blood flow in the activated region and decrease of desoxygenated haemoglobin in the surrounding microvasculature. This mechanism is termed neurovascular coupling – which can vary in normal aging or disease (D'Esposito, Deouell, & Gazzaley, 2003; Fabiani et al., 2014). In stroke patients the relationship

between blood flow and oxygen concentration may be altered and therefore induces an abnormal BOLD signal leading to inaccurate results and conclusions (Carusone, Srinivasan, Gitelman, Mesulam, & Parrish, 2002; Hamzei, Knab, Weiller, & Röther, 2003; Handwerker, Gonzalez-Castillo, E'Esposito, & Bandettini, 2012; Murata et al., 2006). Other studies present evidence that the BOLD signal can be changed by the main risk factors for cerebrovascular disease: hypertension, diabetes and hypercholesterolemia (D'Esposito, Deouell & Gazzaley, 2003; Sobey, 2001). The best way to deal with an altered BOLD signal is to explore the obtained data and to make careful assumptions and conclusions (Handwerker, Gonzalez-Castillo, E'Esposito, & Bandettini, 2012). Hence, the BOLD contrast is still a useful and effective tool to investigate brain function, but caution is suggested when obtaining data from participants with possibly altered neurovascular coupling (He, Snyder, Vincent, Epstein, Shulman, & Corbetta, 2007).

All experiments conducted in the present dissertation are presented in manuscript style, including a short review of relevant literature and a discussion of the results. The last chapter 'Discussion and Conclusion' presents a general discussion of all results and a final conclusion. For reasons of clarity all figures and tables are numbered continuously (with chapter numbers) and the entire literature is presented at the end in the section 'References'.

Manuscripts

"After having described these lesions, and researched their nature, seat, and anatomical progression, it is important to compare these results with those of clinical observation, to finally establish, if possible, a connection between the symptoms and the material disorders."

Paul Broca

6. Musical, visual and cognitive deficits after middle cerebral artery infarction

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Abstract

The perception of music can be impaired after a stroke. This dysfunction is called amusia and amusia patients often also show deficits in visual abilities, language, memory, learning, and attention. The current study investigated whether deficits in music perception are selective for musical input or generalize to other perceptual abilities. Additionally, we tested the hypothesis that deficits in working memory or attention account for impairments in music perception. Twenty stroke patients with small infarctions in the supply area of the middle cerebral artery were investigated with tests for music and visual perception, categorization, neglect, working memory and attention. Two amusia patients with selective deficits in music perception and pronounced lesions were identified. Working memory and attention deficits were highly correlated across the patient group but no correlation with musical abilities was obtained. Lesion analysis revealed that lesions in small areas of the putamen and globus pallidus were connected to a rhythm perception deficit. We conclude that neither a general perceptual deficit nor a minor domain general deficit can account for impairments in the music perception task. But we find support for the modular organization of the music perception network with brain areas specialized for musical functions as musical deficits were not correlated to any other impairment.

6.1 Introduction

The perception, recognition, and joyful sensation of music can be affected by a stroke – a condition called acquired amusia. Impairments of music perception are widely reported in the literature (Ayotte, Peretz, Rousseau, Bard, & Bojanowski, 2000; Liegéois-Chauvel, Peretz, Babaï, Laguitton, & Chauvel, 1998; Mendez & Geehan, 1988; Quensel & Pfeifer, 1923; Tramo, Bharucha, & Musiek, 1990) and can occur after lesions to temporal, frontal, and parietal areas (Botez & Wertheim, 1959; DiPietro, Laganaro, Leemann, & Schnider, 2004; Eustache, Lechevalier, Viader, & Lambert, 1990; Griffiths, 1997; Johkura, Matsumoto, Hasegawa, & Kuroiwa, 1998; Patel, Peretz, Tramo, & Labreque, 1998; Peretz et al., 1994; Piccirilli, Sciarma, & Luzzi, 2000; Satoh et al., 2005; Schuppert, Münte, Wieringa, & Altenmüler, 2000; Steinke et al., 2001; Särkärmö, 2009), but also after subcortical lesions (Hochman & Abrams, 2014). These patient studies showed a double dissociation between melody (Griffiths et al., 1997; Peretz, 1990; Schuppert et al., 2000; Zatorre, 1985) and rhythm perception (DiPietro et al., 2004; Peretz, 1990; Schuppert et al., 2000; Vignolo, 2003).

This double dissociation was supported by recent models for music perception suggesting a highly complex and distributed network of temporal, frontal, and parietal areas, additional to subcortical and limbic structures (Clark, Golden & Warren, 2015; García-Casares, Berthier Torres, Froudist Walsh, & González-Santos, 2013; Koelsch, 2011; Peretz & Coltheart, 2003; Stewart, von Kriegstein, Warren, & Griffiths, 2006). Melodic information is supposed to be mainly processed in superior temporal and frontal areas; the cerebellum and basal ganglia are thought to be involved in processing rhythmic material. Other studies strengthen the role of premotor and supplementary motor areas in beat perception (Fedorenko, McDermott, Norman-Haignere, & Kanwisher, 2012; Grahn & Brett, 2009; Zatorre, Chen & Penhune, 2007). Furthermore functions of pitch and contour processing as well as rhythm perception are attributed to the parietal lobe (Foster & Zatorre, 2009; Lee, Janata, Frost, Hanke, & Granger, 2011; Schwenzer & Mathiak, 2011; Thaut, Trimarchi & Parsons, 2014).

This network widely overlaps with areas usually responsible for domain-general attention and working memory (Janata, Tillmann & Bharucha, 2002). This knowledge is expanded by findings that amusia patients often show deficits in visual-spatial abilities, executive functions, memory, learning, and attention (DiPietro et al., 2004; Griffiths et al., 1997; Särkämö et al., 2009a, Särkämö et al., 2009b). Furthermore music perception problems seem to be highly correlated with aphasia (Stewart et al., 2006; Schuppert et al., 2000, Särkärmö, 2009) and to visuo-spatial neglect (Särkärmö, 2009). Conclusively, a direct link

between music perception and other cognitive functions, as well as even visual abilities, has been suggested.

Särkärmö and colleagues (2009) measured a large group of amusia patients after stroke who presented several cognitive deficits, primarily in attention, working memory (WM), and executive functions. Their work underlined the close relationship between amusia and other cognitive deficits. However, the question whether these connected deficits arise because music perception and the other cognitive functions are accomplished by shared neural processes or whether they involve functionally different but anatomically close areas could not be answered. Lesions in the amusic group were significantly larger than in the non-amusic group and therefore might have mediated the results. Additionally, deficits in attention and WM may have accounted for the poor performance in the music perception task of the amusic patients. The Montreal Battery of Evaluation of Amusia (Peretz, Champod & Hyde, 2003) was used in this study and the selected tasks require relatively good WM, attention, and executive abilities (Särkärmö et al., 2009).

In the current study we wanted to investigate whether symptoms of amusia are specific for musical material or whether a general perceptual deficit can explain the symptoms. Furthermore we were interested in the question whether or not impairments in general domain specific functions like WM or attention could account for poor performances in the MBEA. For this aim we specifically measured stroke patients with small cerebral artery infarctions in order to control for lesions possibly damaging a large array of areas and functions. We applied a large battery of neuropsychological and psychophysical tests including the Montreal Battery of Evaluation of Amusia and tests for visual perception, categorization, neglect, and cognitive functions of attention and WM. Our sample of patients suffering subacute stroke in supply areas of the middle cerebral artery showed a variety of initial symptoms including aphasia, paresis, sensory deficits, and also visual symptoms. Performances in different tests were compared via correlation analysis and Chi^2 statistics were applied to compare subgroups of patients.

6.2 Material and Methods

6.2.1 Ethical Approval

This study was approved by the local ethics committee of the University of Bremen. Subjects were informed about the aim and procedure of the experiment and had to sign a written consent form according to the Declaration of Helsinki. They were free to withdraw from the study at any time.

6.2.2 Subjects

Patients (n= 20) were ten female and ten male volunteers suffering a subacute stroke in supply areas of the medial cerebral artery. Patients were tested one to six days after the stroke onset in the stroke-unit of the central hospital in Bremen. The mean age was 52 years (±9.8) and all of them were right-handed. Exclusion criteria were previous neurological, psychiatric or ophthalmological disorders and auditory defects. Further exclusion criteria for the stroke patients were bleedings, bilateral and previous lesions.

6.2.3 Clinical Investigations

All patients underwent a series of neuropsychological tests, including assessment of visual neglect and extinction, visual fields, stereoscopic vision, color vision, and hearing.

The visual neglect tests included: a line bisection test (Wilson, Cockburn & Halligan, 1987), the apple test (Bickerton, Samson, Williamson, & Humphreys, 2011), the clock task (Ishiai, Sugishita, Ichikawa, Gono, & Watabiki, 1993), and a copying task (target: flower). For assessment of visual field defects static perimetry of 30° of the visual field was conducted with the contralesional eye. The Lang Test (Lang, 1983) and the Ishihara Colour Vision test (Ishihara, 1986) served as measures for stereoscopic and color vision. An audiometry with 8 frequencies for each ear was applied for assessment of hearing.

Furthermore, patients were asked for impairments in the following domains: memory deficits, anomia, reading deficits, visual field defects, spatial orienting disorder and auditory impairments in relation to loudness, sound, voice, and music perception.

All following computer-based tests were performed at 60cm distance from the screen and subjects wore headphones when required (Sennheiser HD 201). Spatial resolution of the monitor (Samsung Sync Master 1100 MB) was 1600x1200 pixels (2041x1617 arcmin) and the temporal resolution was 75 Hz. The fixation dot in each test had a size of 5 arcmin. Response time was ‘infinite’, i.e. the next trial started only after a response was given (enforced response).

6.2.4 Attention Test

The D2 Concentration Endurance Test (Brickenkamp, 1994) is a test for assessing sustained attention and visual scanning ability. It is a paper and pencil task, where subjects are required to cross out targets and leave non-targets untagged with a time constraint of 20 sec for each row (14 rows and 47 characters per row). To measure the quality of performance (correctly processed characters) for each subject the overall number of processed characters, omissions, and errors were evaluated.

6.2.5 Montreal Battery of Evaluation of Amusia

Stimuli

In order to compute a computer-based version of the Montreal Battery of Evaluation of Amusia (Peretz, Champod & Hyde, 2003; MBEA) stimuli were taken from the original version. The subtests 'scale' and 'rhythm' with thirty trials each were used for this experiment. Each trial consisted of a target melody and a comparison melody and both subtests included 15 same and 15 different trials. In 'different' trials, one tone was in a different scale or the rhythm of two subsequent tones was changed (for further information see Peretz, Champod & Hyde, 2003).

Experimental Procedure

Two practice trials were completed in advance, in case of difficulties the examples were played for several times until the subjects understood the procedure of the test. Subjects were told to listen to the melody pairs and to decide whether the melody pair was identical or different (two-alternative-forced choice). Each trial began with a 3-second inter-trial interval while the word 'break' was displayed on the computer screen. Then a melody pair with a 2-second silent interval was played to the subjects while a note was shown on the screen. Answers were given via button press; buttons were held in both hands (one for same, one for different; button position permuted across subjects). Subjects were allowed to press the button while the music was still playing (e.g. as soon as they heard the different tone they were allowed to press the button for 'different') or after the trial.

6.2.6 Visual Gestalt Perception Test

Some of the reported cases of amusic patients showed visual deficits as well. To test similar visual abilities comparable to the MBEA a visual Gestalt perception task was developed in-house.

Stimuli

The Gestalt images consisted of (68x43) Gabor elements distributed over the entire screen while 31-33 of them yield a Gestalt shape by aligned elements. Five Gestalts have been produced by patterns used in the L-POST test (Torfs, Vancleef, Lafosse, Wagemans & de-Wit, 2014). Picture size was 1600x1200px and the Gestalt shapes extended over 6.5x6.5° of visual angle, placed centrally in an area of 10.5x10.5° of visual angle (Figure 6.1). There were two levels of difficulty: easy (perfectly aligned) and difficult (Gabor elements rotated by up to 15 degrees). The whole task consisted of 40 trials: 20 same and 20 different trials,

each containing ten difficult and ten easy comparisons. For each comparison it was ensured that the Gestalt was not placed at the exact same position on both pictures.

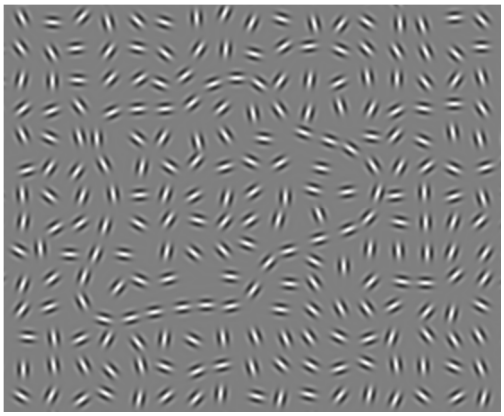

Figure 6.1: Example image for Gestalt perception task (Gabor shape cropped out for visualization).

Experimental Procedure

Before the test, five practice trials were completed to familiarize the subjects with the task. Each trial started with 1000ms fixation (red dot on grey background). Then target and comparison pictures were shown for 100ms with a 1000ms inter-stimulus interval. After that a green fixation point was shown to indicate that the answer was expected. Subjects were instructed to carefully watch the presented pairs of shapes and to decide whether or not the shapes were identical (two-alternative-forced choice). Answers were given via button press (as for the MBEA task).

6.2.7 Categorization

Because of the reported deficits in visual abilities and language (DiPietro et al., 2004; Griffiths et al., 1997; Stewart et al., 2006; Schuppert et al., 2000; Särkämö et al., 2009a; Särkärmö et al., 2009b), a categorization task consisting of visual and language-related material was invented. In order to investigate whether deficits were present in only one modality or in several, the test consisted of four different elements: visual and auditory material as well as verbal and nonverbal stimuli.

Stimuli

The categorization task consisted of 56 stimuli (28 animals and means of transportation each). The task was repeated four times in both visual and auditory modalities (written words, spoken words, images, sounds). Chosen stimuli were controlled for word length, number of syllables and frequency in German language.

Sounds were animals and means of transportation sounds cut to the duration of 700ms. Only the sound of the corresponding animal/means of transportation was presented to the

subjects and loudness was corrected for all trials. Spoken words had the duration of 295 – 912ms (mean: 528ms).

Images were extracted pictures of animals or means of transportation on a square grey background (11.4x11.4°). The extracted pictures were placed centrally in an area of 5.7x5.7° of visual angle (Figure 6.2). Written words where presented in black on a white background (11.4x11.4°) and the words were placed centrally in an area of 8.5x0.95° of visual angle which corresponds to a font size of 48pt (Figure 6.3).

Figure 6.2: Example image for categorization and two-back task.

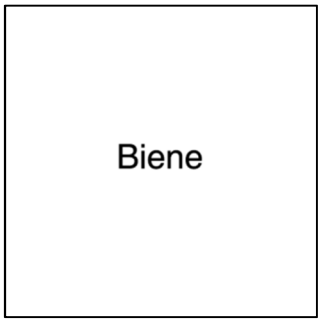

Figure 6.3: Example image for a word in the categorization task, with black border for visualization.

Experimental Procedure

Each trial started with a 1000ms fixation where a red fixation dot on a grey background had appeared. Stimulus presentation was different for each modality (images: 50ms; written words: 60ms; sounds: 700ms; spoken words: 295 – 912ms depending on the word length). A visual mask was applied for 300ms after stimulus presentation for the visual trials. During auditory stimulation a grey screen was displayed to the subject. Subjects were instructed to decide whether the seen or heard stimulus belongs to the category ‘animal’ or ‘means of transportation’ and to indicate the answer via button press (green: animal, red: means of transportation; button position permuted across subjects). The inter-trial-interval was 500ms.

6.2.8 Two-Back Task (WM)

Stimuli

The two-back task consisted of a visual subtest (pictures, Figure 6.2) and an auditory subtest (sounds). Stimuli were chosen from the categorization stimuli, but only five animals and five means of transportation were included in the task (different ones for each modality).

Experimental Procedure

Each trial started with 500ms fixation where a red fixation dot on a grey background was shown. Stimulus presentation of 500ms and response time of 1000ms followed. During response time a grey screen was shown. The inter-trial-interval was 500ms. Subjects were instructed to carefully listen to/look at the presented stimuli and to press a button whenever the presented one was the same as the second last (two-back) one (Go-No Go task). They were allowed to press the button during stimulus presentation or during the response time. The whole experiment consisted of 64 trials with 20 target trials.

6.2.9 Data Analysis

Performance (number correct of answers) of all computer-based tasks and the attention test were analyzed using IBM SPSS Statistics 23. The analysis of the relationships between music and Gestalt perception, attention, categorization, and WM was based on a correlation analysis (Pearson, two-tailed, Bonferroni-corrected). A Chi^2 statistics was applied on the distribution of impairments across subgroups of patients. For this aim groups were assigned according to 'deficit' versus 'no deficit'. After group assignment, the Chi^2 test compared deficits across all other tasks to detect similarities across different tasks. This was done for five groups: for 1) music perception, 2) visual Gestalt perception, 3) categorization, 4) attention, and 5) WM.

Lesion Analysis

Lesion analysis was performed with MRI images obtained when patients were admitted to the stroke unit. MRIcron (Rorden, Karnath, & Bonilha, 2007) and the clinical toolbox of SPM (Rorden, Bonilha, Fridriksson, Bender, & Karnath, 2012) served to delineate and normalize lesions of nineteen patients (Patient P12 only had a cCT measurement). The MNI Flair template brain was used for normalization.

6.3 Results

6.3.1 Basic Investigations

Initial symptoms reported by the patients are displayed in Table 6.1. Aphasia and Paresis were the most common symptoms in this patient population. In the measurement session a few patients reported still existing anomia (8), memory deficits (5), reading disorders (4) and auditory deficits concerning loudness (2). No visual or spatial orienting disorders were reported.

Table 6.1: Initial symptoms of patients in decreasing order of frequency

	All Patients	Left-hemispheric	Right-hemispheric
N	20	13	7
Aphasia	10	9	1
Paresis	9	6	3
Nausea	7	5	2
Headache	6	5	1
Sensory impairments	6	3	3
Confusion	3	3	0
Amnesia	3	2	1
Visual symptoms	2	2	0

Extinction was not present in the group of patients, but one neglect patient (P13) was identified showing abnormal neglect-typical responses in three of four neglect tests (clock task was normal). Color vision was normal in the patient sample, but six patients showed problems in stereoscopic vision (three minor and three major).

6.3.2 Clinical Investigations

Results for the attention test (D2), MBEA and visual Gestalt tasks, categorization, and WM tests can be seen in table 6.2. The correct numbers of answers are displayed and a cut-off value of 75% was applied in order to detect abnormalities (except for the D2 test where age-corrected norm values are available). For cut-off values for the different tests were 23 for the MBEA (this cut-off value was used in other studies as well), 30 for the visual Gestalt test, 42 for the categorization task, and 15 for the WM test.

Five patients showed deficits in attention, two in musical perception, five in visual Gestalt perception, two in categorization and eleven in the two-back task. The two patients with amusic symptoms (P5 and P6) did not show any other impairment in the applied tests. Both of them reported aphasia as initial symptoms, one (P5) still displayed anomia, reading disorder and reported auditory deficits. The neglect patient (P13) did not show amusic symptoms but deficits in the visual Gestalt task.

Table 6.2: Number of correct answers for the attention test (D2), MBEA and visual Gestalt tasks, categorization (cat) and WM tests for all patients. Impaired performances are highlighted in red (below 75% correct). MBEA 1: scale task; MBEA 2: rhythm task

Patient	Attention D2	MBEA 1	MBEA 2	Gestalt	Cat sounds	Cat pictures	Cat auditory words	Cat visual words	WM visual	WM auditory
1	315	24	26	37	51	47	54	54	7	7
2	310	27	24	29	52	44	55	32	19	15
3	333	28	30	35	48	52	54	53	15	9
4	327	29	28	33	48	54	56	55	20	13
5	316	13	21	36	50	51	56	55	16	15
6	379	26	20	32	45	46	54	49	20	17
7	207	23	24	33	54	49	56	55	12	8
8	287	28	25	18	48	55	55	52	12	13
9	451	26	26	35	49	49	56	52	16	15
10	262	24	30	22	50	49	56	55	17	10
11	390	26	29	29	52	55	56	56	18	16
12	108	23	28	39	50	41	55	49	8	5
13	331	27	28	20	48	47	55	48	16	14
14	367	29	25	34	47	53	56	54	14	14
15	99	25	26	30	51	51	55	44	15	13
16	453	26	24	32	51	52	55	55	19	18
17	477	27	30	37	53	54	56	55	15	17
18	372	27	27	33	47	42	54	55	13	16
19	406	25	27	35	49	52	56	52	18	16
20	408	25	25	34	51	54	55	54	18	16

A correlation analysis (Pearson correlation coefficient, two-tailed, Bonferroni-corrected) for the patient group (of data in Table 6.2) revealed two significant correlations: auditory WM correlated with visual memory ($r=0.728$, $p<0.001$), and with the attention test ($r=0.713$, $p<0.001$).

A group comparison of the impairment distribution between subgroups of patients was performed with a Chi^2 statistics. The group of patients with attention deficits showed a significantly higher incidence of auditory WM deficits ($Chi^2=6.667$, $p=0.01$). A trend was observed for the group with attention deficits and their incidence in visual WM deficits ($Chi^2=2.857$, $p=0.09$). A look at the data showed that all patients with attention deficit had impairments in the auditory two-back task and that three of five also showed visual WM deficits. No other significant Chi^2 results were obtained.

6.3.3 Lesion Data

Lesion overlap in the patient sample was relatively small, except for lesions in the basal ganglia (Figure 6.4). Amusia patients presented a left frontal lesion (P5) and a right basal ganglia lesion (P6).

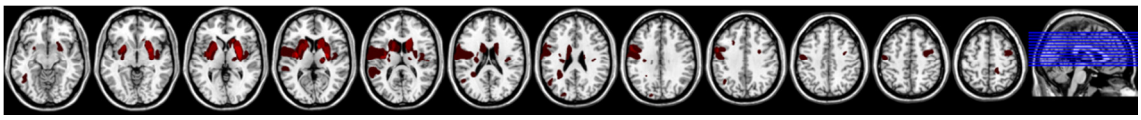

Figure 6.4: Lesion overview: Normalized lesions of nineteen patients (left on left and right on right side). Bright red areas are associated with maximum lesion overlap.

Patient P6 showed amusia symptoms and a lesion in the right basal ganglia. Two other patients with right basal ganglia infarction but without amusia symptoms were identified: patients P11 and P19. A subtraction plot revealed relatively small and circumscribed areas of the putamen and the globus pallidus of the basal ganglia associated with rhythm deficit amusia (Figure 6.5). The caudate nucleus seems not to be connected to the music perception deficit.

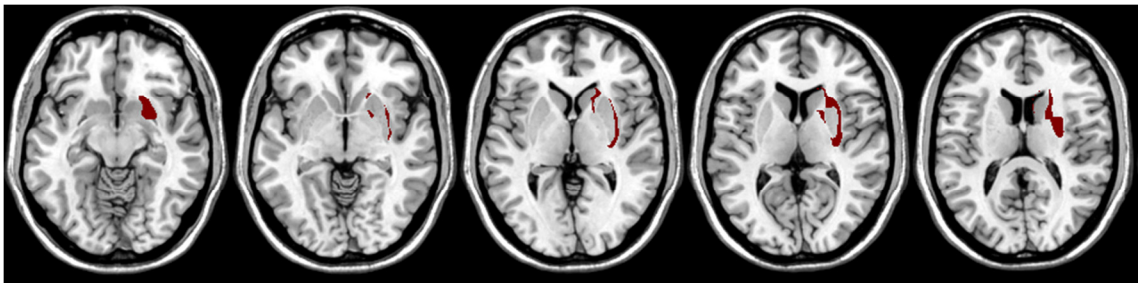

Figure 6.5: Basal ganglia lesion subtraction plot: Amusia patient P6 minus two non-amusic patients with basal ganglia infarction.

6.4 Discussion

This study was carried out in order to investigate whether symptoms of amusia are music selective or whether they can be explained by (1) general perceptual deficits or (2) impairments in attention or WM.

6.4.1 Music perception deficits

We present data from twenty patients suffering middle cerebral artery infarction with typical initial symptoms and subjective impairments. In this sample, only two amusia patients were identified and they did not show any other deficits in the applied assessment. We infer that amusia is not necessarily connected to impairments in domain general cognitive functions or to other perceptual deficits per se, as we present two cases with selective deficits in the MBEA and relatively pronounced cortical lesions (frontal lobe and basal ganglia).

Both amusia patients presented initial aphasic symptoms, the more severe amusia patient showed still existing reading disorder and anomia as subjective impairments during testing. Aphasia and music perception deficits seem to be connected in our study as well, in line with previous literature (Stewart et al., 2006; Schuppert et al., 2000, Särkärmö, 2009). Furthermore, the double dissociation was also visible in our sample, which shows that it is very important to test both rhythmic and melodic abilities (DiPietro et al., 2004; Griffiths et al., 1997; Peretz, 1990; Schuppert et al., 2000; Vignolo, 2003; Zatorre, 1985). Our patient group did comprise one patient suffering hemi-spatial neglect and he did not show any impairment in music perception. Thus, neglect is not always associated with amusia which is in contrast to Särkärmö (2009).

6.4.2 Anatomical correlates of amusia

Patient P6 presented right basal ganglia lesion and rhythm perception deficits. This is in line with a study investigating stroke patients with damage in the basal ganglia who showed difficulties detecting beat or rhythm-based differences in melodies (Schwartze, Keller, Patel & Kotz, 2011). The lesion analysis of patient P6 and other stroke patients with lesions in the right basal ganglia revealed that the putamen and globus pallidus were associated with a deficit in rhythm perception, while the caudate nucleus was not. Lesions in the left basal ganglia did not lead to amusic symptoms although the lesions were distributed relatively similar on both hemispheres. Two possible conclusions come to mind: 1) Either only right hemispheric basal ganglia lesions of the specific regions lead to amusic symptoms or 2) individual differences in the representation of music perception complicate this view about the music perception network and its dysfunctions. Other studies indeed showed results supporting highly individual representations of the music

perception network (Schuppert et al., 2000; Toiviainen, Alluri, Brattico, Wallentin & Vuust, 2014). In contrast, Schwartze and colleagues (2011) presented a group of patients with basal ganglia lesions in both hemispheres. Group results showed a significant impairment compared to healthy controls. Unfortunately, this study only presented results on the group level and no further distinction between lesion sites of their patients was made. Therefore, one cannot exclude that only a few patients in the patient group presented deficits, severe enough to induce significant differences compared to the control sample. A lesion analysis of this patient group and their behavioral results may further contribute to this issue. Other studies also present a clear relationship between basal ganglia damage and rhythm perception deficits, e.g. in Parkinson's patients (Grahn & Brett, 2009; Merchant, Luciana, Hooper, Majestic, & Tuite, 2008). Thus, there is clear evidence that the basal ganglia engage in rhythm perception. But at present, no final differentiation between both possible explanations (lateralization vs. individualization) can be made. Additional work about basal ganglia infarctions and music perception deficits are needed to further investigate this issue.

6.4.3 Other deficits

Generally, we found only few deficits in categorization abilities, and a few more patients suffering visual Gestalt perception deficits. Attention and WM were impaired in five and eleven patients respectively and a strong correlation between both abilities was shown by correlation and Chi^2 statistics. On the other hand, no correlations between performances of other tasks were found.

This shows that deficits in attention and WM, which occurred relatively often, were connected to each other but cannot account for low performances in the MBEA. Our patients with low performance in attention and WM tests were still able to solve the MBEA. Additionally, visual perception deficits were not associated with musical deficits or vice versa. Therefore, the hypothesis that deficits in the MBEA may be explained by a general perceptual dysfunction or domain general deficits have to be rejected. Although cognitive load of the MBEA is relatively high (Särkämö et al., 2009), it is not sensitive to minor impairments in domain general cognitive functions (like those in our patients). Whether or not major impairments influence performance in the MBEA remains to be investigated.

6.4.4 Conclusion

Our study shows that amusia is not necessarily connected to other deficits in perceptual or cognitive functions or to neglect. Previous results may have been mediated by increased lesion size of amusic patients (Särkämö, 2009a). In contrast the lesions of our patient

sample were relatively pronounced. One may infer that the increased lesions damaged several areas responsible for different functions and that in our study the small lesions damaged exactly the specific area important for music perception (functionally distinct but anatomical close).

Important regions seem to be the putamen and the globus pallidus as lesion in these areas induced rhythm perception deficits. The question whether this deficit is associated with lesions only in right hemispheric infarctions or whether individual differences account for the results cannot finally be answered.

Our findings of patients with selective deficits and pronounced lesions support the view of a modular organization of the music perception network (Peretz & Coltheart, 2003; Piccirilli, Sciarma, & Luzzi, 2000). We found patients with selective deficits not connected to other deficits supporting the theory of specific sub-modules in distinct brain areas that are specialized for musical functions.

6.4.5 Limitations

For this study twenty-five stroke patients were screened with the MBEA to look for music perception deficits. Only two amusic stroke patients were identified. Full data were only available for the twenty subjects presented here. The lesion overlap in this study was small. However, it was intended to specifically test patients with small lesions to avoid the danger of large lesions that have an increased risk to damage a large array of functions. The mean age of stroke patients in the study by Särkämö et al (2009) was 56 and 60 years for both groups. Our patient group had a mean age of 52 years. The younger age may have induced less severe deficits or faster recovery, which we could not control for. Additionally, differences between patients may be due to demographic or clinical values we did not access.

Nevertheless, the results can make a significant contribution to what is already known about the music perception network and acquired amusia.

7. Amusia after stroke – an fMRI study

Stephanie Rosemann, Peter Erhard, & Manfred Fahle

Submitted to *Music Perception*

Abstract

The network which is responsible for processing music is widely distributed in the brain. Different brain regions are engaged in different sub-functions, e.g. melody or rhythm perception. This network can be damaged by a stroke leading to a disorder pattern referred to as acquired amusia. A local brain injury may cause abnormal brain function even in intact brain regions which are connected to the lesion. The aim of this study was to investigate the BOLD signal in damaged and intact music processing brain regions of amusia patients. Stroke patients with middle cerebral artery infarctions were tested for music perception deficits. An fMRI experiment consisting of musical stimulation (unimodal and bimodal in combination with visual stimulation) was conducted with healthy participants, stroke patients with amusia, and stroke patients without musical deficits. We found increased activation in occipital, temporal, and postcentral regions in stroke patients compared to healthy participants. Amusia was connected to increased activation in frontal and parietal lobe areas, insula and specifically inferior parietal lobule, and supramarginal gyrus. We argue for compensatory mechanisms in stroke patients recruiting additional brain regions in the unimodal stimulation which was not present for the bimodal condition.

7.1 Introduction

The perception of music is accomplished by a widely distributed non-lateralized network in the brain (Alossa & Castelli, 2009; Peretz & Coltheart, 2003; Schuppert, Münte, Wieringa & Altenmüller, 2000). If one of the cortical areas belonging to the network is damaged, e.g. by a stroke, the perception of music may be impaired and the joyful sensation elicited by music can turn into strange and even uncomfortable sound perception (DiPietro, Laganaro, Leemann & Schnider, 2004; Griffiths, 1997; Mendez & Geehan, 1988; Piccirilli, Sciarma & Luzzi, 2000; Quensel & Pfeifer, 1923). This dysfunction is termed amusia and can be caused by lesions in superior and middle temporal gyri, the insula, inferior parietal lobule or frontal areas (Ayotte, Peretz, Rousseau, Bard, & Bojanowski, 2000; Botez & Wertheim, 1959; DiPietro et al., 2004; Eustache, Lechevalier, Viader & Lambert, 1990; Griffiths, 1997; Hochman & Abrams, 2014; Johkura, Matsumoto, Hasegawa & Kuroiwa, 1998; Liegéois-Chauvel, Peretz, Babaï, Laguitton & Chauvel, 1998; Mendez & Geehan, 1988; Patel, Peretz, Tramo & Labreque, 1998; Peretz et al., 1994; Piccirilli et al., 2000; Satoh et al., 2005; Steinke, Cuddy & Jakobson, 2001). Additionally, Parkinson and stroke patients with damage in the basal ganglia have difficulty detecting beat or rhythm-based differences in melodies (Grahn & Brett, 2009; Merchant, Luciana, Hooper, Majestic, & Tuite, 2008; Schwartze, Keller, Patel & Kotz, 2011). Case studies showed a double dissociation between melody and rhythm perception (DiPietro et al., 2004; Griffiths, 1997; Peretz, 1990; Schuppert et al., 2000; Vignolo, 2003).

Functional magnetic resonance imaging (fMRI) studies with healthy participants showed that mainly frontal cortical areas are responsible for melody processing while the cerebellum and basal ganglia are involved in rhythm perception. The superior temporal cortex plays a role in both melody and rhythm processing (García-Casares, Berthier Torres, Froudist Walsh, & González-Santos, 2013; Koelsch, 2011; Stewart, von Kriegstein, Warren & Griffiths, 2006). Premotor and supplementary motor areas, as well as basal ganglia, engage in beat perception (Fedorenko, McDermott, Norman-Haignere & Kanwisher, 2012; Grahn & Brett, 2009; Zatorre, Chen & Penhune, 2007). The perception of different rhythmic structures is achieved by several brain regions in frontal, parietal, and temporal cortices (Thaut, Trimarchi & Parsons, 2014). Additionally, parietal areas are involved in pitch and contour processing and discrimination (Foster & Zatorre, 2009; Lee, Janata, Frost, Hanke & Granger, 2011; Schwenzer & Mathiak, 2011). Attentive listening to music recruits a network of frontal, temporal, and parietal areas, brain regions usually involved in domain-general attention and working memory (Janata, Tillmann & Bharucha, 2002).

Recently, music perception deficits after stroke in the supply area of the middle cerebral artery have been described repeatedly in the literature (Hochman & Abrams, 2014; Kohlmetz, Altenmüller, Schuppert, Wieringa, & Münte, 2001; Münte et al., 1998; Särkämö et al., 2009; Särkämö et al., 2010) and therefore receive growing attention. However, with the current knowledge an allocation of the deficit to a circumscribed area of the brain seems to be demanding because the network of music processing is widely distributed and different brain regions engage in specific sub-functions. Furthermore, the effects of a focal brain lesion in the music processing network on other areas in the network are not known yet. From the literature it becomes obvious that brain areas that are supposed to be involved in healthy music processing and brain lesions leading to amusia symptoms do not always match. A first step to explore the influence of a focal brain lesion on other music processing regions seems to be an fMRI study with amusia patients – which to our knowledge has not been performed so far. By this method a comparison to the music processing network of healthy participants (identified by previous fMRI studies) can be achieved as well.

Other neuronal networks of the brain have already been shown to change not only in the area of the brain damage itself but also in connected but structurally intact regions (Karnath et al., 2005). Focal brain injury can lead to global functional changes if the damaged brain areas are connected and communicating with other brain areas in that network (Gratton, Nomura, Pèrez & D'Esposito, 2012). In hemiparetic stroke patients greater and more widespread activation was found in early compared to late stages after stroke (Calautti, Leroy, Guincestre, Mariè & Baron, 2001a; Feydy et al., 2002; Grefkes et al., 2007; Marshall et al., 2000; Meehan, Randhawa, Wessel & Boyd, 2011; Ward, Brown, Thompson & Frackowiak, 2003). This additional recruitment is thought to be compensatory and it decreases as motor function recovers.

Based on the findings that a) a local brain injury could cause widespread disturbances in brain function and activation in connected but intact brain areas and b) music processing is achieved by a distributed network in the brain, our objective was to investigate the effects of a lesion leading to amusic symptoms on other brain regions belonging to the music perception network. More specifically, we were interested in whether or not amusia patients show an abnormal BOLD signal in intact brain regions associated with music processing (temporal and frontal lobes, cerebellum, and basal ganglia). Therefore stroke patients with middle cerebral artery infarctions were screened for music perception deficits. An fMRI experiment was conducted in healthy participants, stroke patients with musical deficits, and stroke patients without musical impairments to assess the BOLD

signal changes with respect to passive music listening (unimodal and also in combination with visual input).

7.2 Material and Methods

7.2.1 Ethical Approval

This study was approved by the local ethics committee of the University of Bremen. Participants were informed about the aim and procedure of the experiment and had to sign a written consent form according to the Declaration of Helsinki. They were free to withdraw from the study at any time and they were paid for participation.

7.2.2 Stroke Patients

Stroke patients suffering a stroke in supply areas of the medial cerebral artery participated in this study. The group consisted of nine participants, three female and six male participants within the age range of 32 to 65 years, with a mean age of 52.6 (±9.3) years. Patients with bleedings, bilateral and previous lesions were excluded from the study.

All patients participated in a behavioral study one to four days after their stroke. In this study they conducted the Montreal Battery of Evaluation of Amusia (MBEA; Peretz, Champod & Hyde, 2003) – melody and rhythm perception were included – and a test for visual Gestalt perception (developed in-house). Two amusia patients were identified (P2 and P3). Patient P2 was particularly interesting because he showed amusia symptoms and participated in the fMRI experiment only ten days after the stroke. Moreover, he participated in a re-test of imaging and behavior six months after the stroke as well.

7.2.3 Participants

Age-matched healthy control participants with a mean age of 53.7 (±10.1) years participated in this study as well.

All participants and patients were native German speakers and right-handed. Exclusion criteria for patients and participants were previous neurological, psychiatric or ophthalmological disorders, and auditory defects.

7.2.4 Stimuli

Stimuli consisted of video sequences of a German Musical song (Musical Elisabeth, Song: ‘So wie du’; DVD Live aus dem Theater an der Wien, 2005). Each of the six video sequences was presented four times (twenty-four stimulation sequences in total): unimodal visual presentation, unimodal auditory presentation, bimodal synchronous visual and auditory presentation, and bimodal asynchronous visual and auditory presentation with the visual

being 560ms ahead of the auditory presentation (the latter not evaluated here). During auditory only presentation a green fixation point on a grey background and during the rest condition a red fixation point on a grey background was presented. Image size for unimodal visual and bimodal presentation was adjusted to 9.72° x 6.92° of visual angle and the videos were presented centrally. Participants were instructed to fixate on the fixation point whenever it was present (rest condition and auditory stimulation) and to freely watch all visual stimuli (video sequences). No response or interaction by volunteers was expected.

Visual stimuli were presented by a projector (DLA-G15E, JVC Professional, Japan) retrofitted with a custom lens on a screen which was positioned behind the scanner at a distance of 140cm from eye to screen. Participants lay in the scanner with lights off and they were able to look at the stimuli via a mirror which was attached to the head coil. Auditory stimuli were presented via MR compatible headphones (CONFON HP-SC 02, MR confon GmbH, Germany) which the participants wore for the whole measurement session.

7.2.5 Data Acquisition

We used a 3T whole-body Siemens Magnetom Skyra MRI machine with a 20 channel receive only head coil for scanning. Participants performed one functional run, a T1-weighted anatomical scan and a T2-weighted anatomical scan in one session. Functional images were acquired using an interleaved and ascending echo-planar imaging (EPI) sequence (TR = 2500 ms, TE = 30 ms, flip angle = 83°, slice thickness 3mm, 46 slices, 192x192 mm2). The T2-weighted images were collected to localize the lesions in patients and to check for structural abnormalities in controls (TR = 4280 ms, TE = 9.4 ms, flip angle = 120°, slice thickness 3mm, 40 slices). Structural images were acquired with a 3-D T1-weighted sequence (MP-RAGE, TR = 1900, TE = 2.07, flip angle = 9°, slice thickness 1mm, 176 sagittal slices).

7.2.6 Experimental Procedure

For each participant one functional run was conducted. Twenty-four stimulation sequences (consisting of the different unimodal and bimodal conditions) with a duration of 20 seconds each were presented with a resting condition of 10 seconds in between. In total, the experiment lasted for 12 minutes. Before the experiment the participants completed a practice trial where all four conditions (visual, auditory, synchronous bimodal, and asynchronous bimodal stimulation) were presented consisting of four video sequences of another song from the same Musical. The practice trial had the duration of one minute (4 times 10 seconds presentation, 4 times 5 seconds resting condition).

To control fixation and eye movements an eye-tracking system was used that recorded one eye of the participant via the mirror above the participant's head during the experiment. Eye tracking data acquisition and stimuli presentation was achieved by in-house software based on Matlab (Matlab 2013a, The MathWorks, Inc., USA).

7.2.7 Data Analysis

We analyzed the imaging data with the Statistical Parametric Mapping software package (SPM8, Welcome Department of Imaging Neuroscience, London, UK) based on Matlab 2013a. Preprocessing of each dataset included slice-timing offset correction, realignment estimation, normalization to the Montreal Neurological Institute (MNI) stereotactic space, and Gaussian smoothing (full width half maximum = 8mm). In the first level analysis, a temporal high pass filter (128s) was applied. Head movement parameters were entered as regressors and different conditions were individually modeled by the canonical hemodynamic response function. Three contrasts were computed on the individual level: a) auditory vs. rest, b) visual vs. rest and, c) bimodal synchronous stimulation (video) vs. rest. In the following the contrasts will be referred to as a) auditory, b) visual, and c) video. Statistical threshold was set to $p<0.001$ (uncorrected). As we had only nine participants in each group and the patient group was very inhomogeneous, we examined individual data and did not perform a second-level analysis. For the individual analysis we determined the activated regions for each participant and each contrast. We extracted the number of activation foci (maximally 30 foci, 8mm apart) and the number of activated voxels per region from the SPM statistics output for all participants.

Based on individual results (activated anatomical regions, number of foci, and number of activated voxels) a group analysis was performed via Chi^2 and T-statistics with SPSS (IBM SPSS Statistics 23). For patient P2 a separate analysis was computed to compare his voxel based results with the results of the group according to the method suggested by Crawford (Crawford & Garthwaite, 2002; Crawford & Howell, 1998).

7.3 Results

This study was carried out to investigate functional correlates of amusia. Stroke patients with amusic symptoms, stroke patients without amusic symptoms, and healthy participants were investigated with fMRI to assess the BOLD signal in brain areas associated with music processing.

7.3.1 Clinical Evaluation of Stroke Patients

Behavioural results and elapsed days between stroke and investigation are listed in Table 7.1. Hence, two amusia patients were included in the study, the other patients served as

'control stroke patients without any deficit' or 'control stroke patients with visual deficit'. Four of the patients were measured in the subacute phase (7 to 10 days after the stroke) and the other five were measured in the subacute-chronic state (> 50 days after the stroke). Additionally, P2 took part in a re-test six months after his stroke (see results under section 'Patient P2').

Table 7.1: Overview of stroke patients: Elapsed days between stroke and fMRI investigation and Behavioral Data acquired few days after the stroke. (Deficits are in bold and shaded in grey, amusia patients are shaded in red)

Patient	Days after stroke	Melody perception	Rhythm perception	Visual Gestalt perception
1	97	29	28	33
2	10	26	**20**	32
3	113	**13**	**21**	36
4	8	28	25	**18**
5	52	23	24	33
6	7	24	30	**22**
7	50	26	26	35
8	105	27	28	**20**
9	8	26	24	32

Stroke locations are shown in Figure 7.1. Patients P2 and P8 suffered from right-hemispheric lesions, all other patients had left-sided lesions.

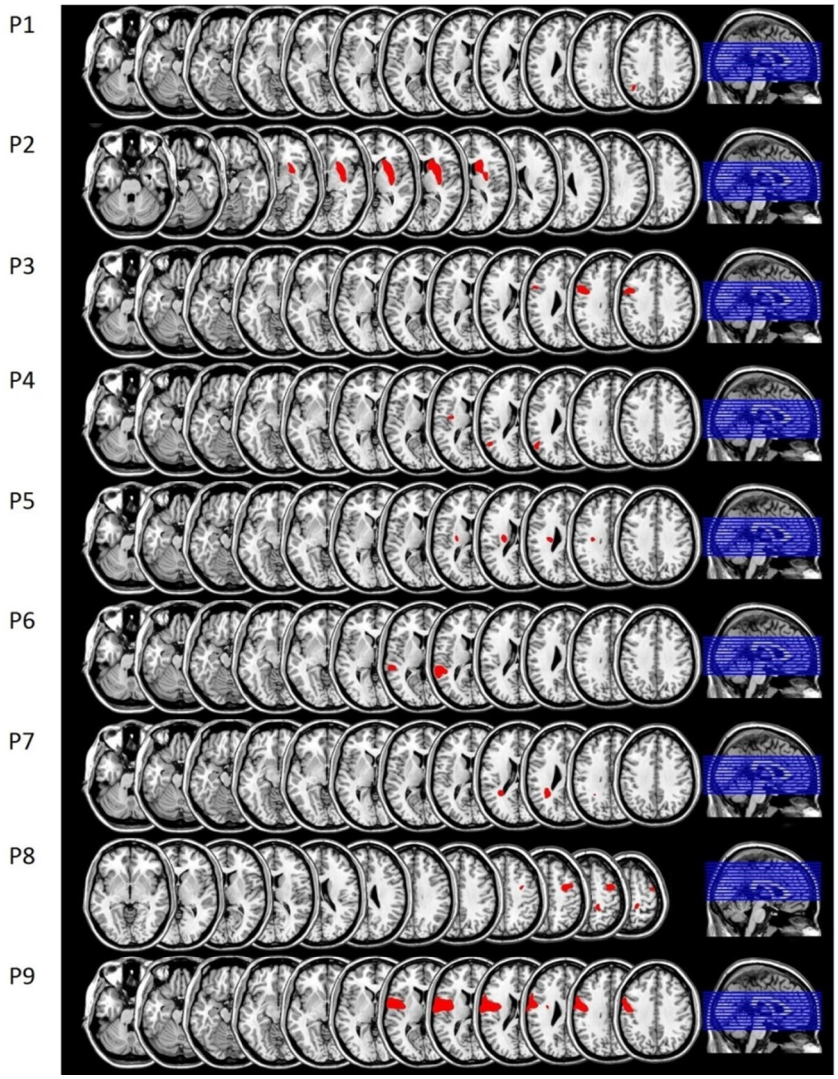

Figure 7.1: Lesions for all patients normalized with MRIcroN and clinical toolbox of SPM (left on left side).

The glass brain views of the three computed contrasts for all patients and participants can be seen in Figure 7.2. The following results section will be divided into three different parts: foci based results, voxel based results, and results of Patient P2 in detail.

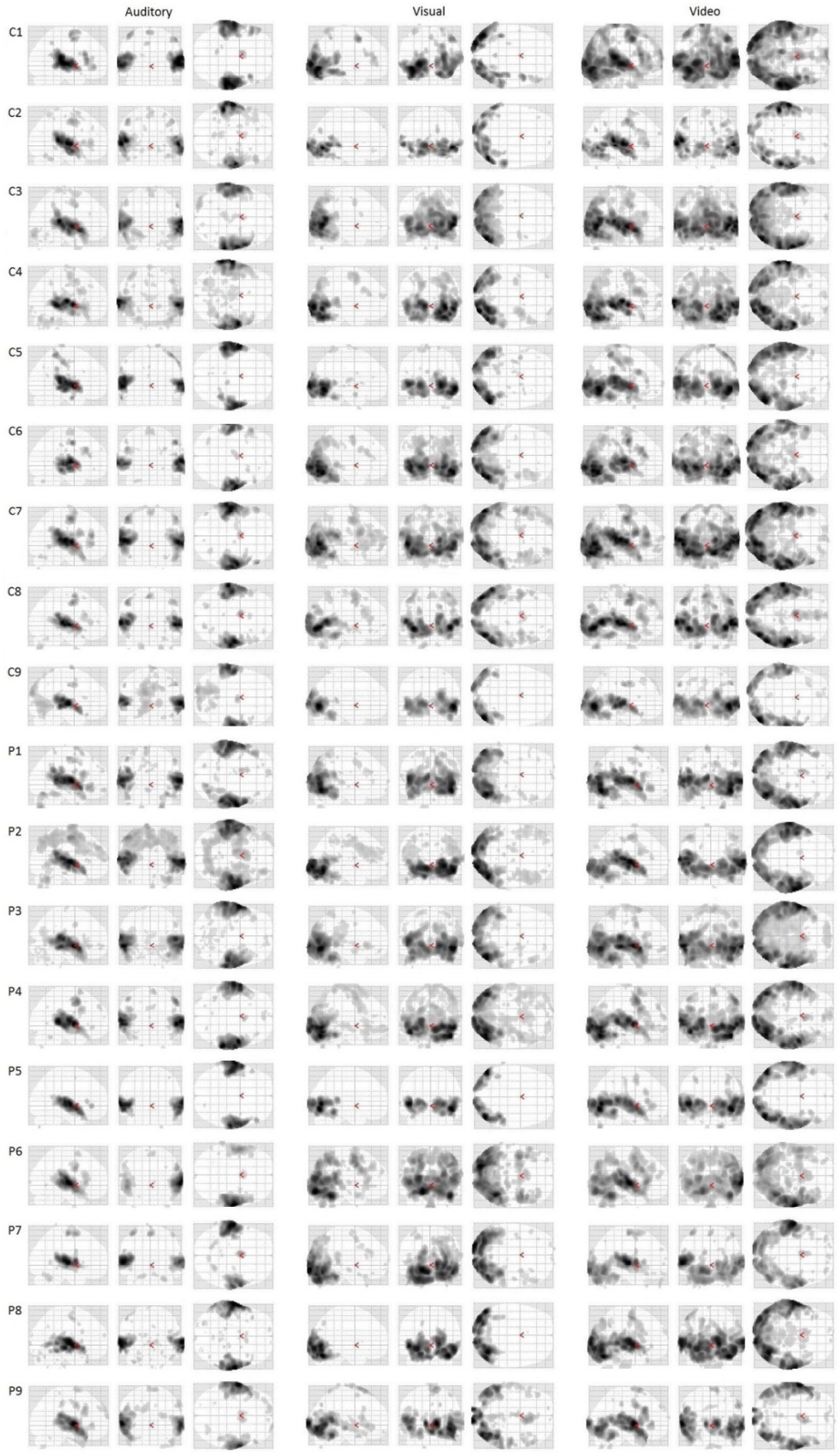

Figure 7.2: Glass brain views of all participants/patients for all computed contrasts (auditory, visual, video), C1-9 denote results for healthy control participants and P1-9 the results for the stroke patients.

7.3.2 Foci-based Analysis

The term 'principal activation' is used to describe whether one participant presented at least one focus of activation in the specific brain region for the given contrast. Tables 7.2 to 7.4 show the number of foci for each participant and for all three computed contrasts.

Contrast auditory (auditory stimulation vs. rest)

In this contrast mainly frontal and temporal areas were activated. We found that 56% up to 100% of the participants showed principal activation in the precentral gyrus, as well as in superior, middle, medial, and inferior frontal gyri. For the superior and middle temporal gyrus 78% to 100% of the participants showed at least one activation focus. Parietal areas like the postcentral gyrus, inferior parietal lobule, and precuneus were principally activated in up to 56% of the participants. Same (up to 56% of the participants) number of activation foci was found for the cerebellum (not shown in tables).

The foci distribution of healthy participants and stroke patients was compared via Chi^2 tests (Fisher's exact test, df=1). For the auditory contrast less stroke patients had at least one activation focus in the right precentral gyrus (p=0.041) and right postcentral gyrus (p=0.066). No significant differences in number of foci between healthy controls and stroke patients were obtained by unpaired one-sided t-tests, i.e. patients were not significantly impaired.

Contrast visual (visual vs. rest)

In the visual contrast signal increases can be found in frontal areas and mainly in the occipital cortex. Only 11% to 78% of the participants – less than for the auditory contrast – showed principal activation in frontal areas, whereas 44% to 100% of the participants had at least one activation focus in middle and inferior occipital gyri, cuneus, fusiform, and lingual gyri. Temporal areas also showed activation for this contrast, mainly middle temporal gyrus (44% – 89%). Postcentral gyrus (22-67%) and superior parietal lobule (22-56%) were the main activation foci in the parietal lobe.

Comparison of foci distribution via Chi^2 tests (Fisher's exact test, df=1) for this contrast indicated that fewer stroke patients showed principal activation in the left precentral gyrus (p=0.025), the left inferior occipital gyrus (p=0.008), and the left cuneus (p=0.052), whereas more stroke patients had at least one activation focus in the right inferior occipital gyrus (p=0.025). The number of foci across both groups was compared via unpaired one-sided t-tests. In this contrast patients had less foci than healthy controls in the precentral gyrus (p=0.037) and the cuneus (p=0.047). Patients showed more activation foci in the medial frontal gyrus (p=0.046).

Contrast video (bimodal synchronous stimulation vs. rest)

For this contrast we found activation throughout the whole brain. Precentral and frontal gyri showed principal activation in 33% up to 100% of the participants. For parietal areas fewer participants with at least one focus were found (11-89%). Occipital gyri and cuneus were principally activated in 11% to 78% of the participants. In 67% to 100% of the participants we found at least one activation focus in the superior and middle temporal gyri. Up to 89% of the participants also showed activation foci in parts of the cerebellum (not shown in tables).

In the video contrast the principal activation in stroke patients compared to healthy controls (tested by Fisher's exact test, df=1) was lower for the right medial frontal gyrus ($p=0.077$) and higher for the right inferior occipital gyrus ($p=0.066$). The number of foci across both groups showed no significant differences (unpaired one-sided t-tests).

Table 7.2: Principal activation denoted by number of foci for each participant (left/right) for the auditory contrast

Anatomical Region	Healthy controls									Stroke patients								
	C1	C2	C3	C4	C5	C6	C7	C8	C9	P1	P2	P3	P4	P5	P6	P7	P8	P9
Precentral Gyrus	1/1	1/2	1/5	1/6	1/2	2/1	1/1	2/1	2/1	1/1	1/0	3/0	2/1	0/0	2/2	3/4	3/0	0/3
Superior Frontal Gyrus	1/0	6/1	1/2	1/2	0/0	2/2	3/1	1/1	0/1	6/2	0/1	0/1	1/2	0/0	1/1	1/0	2/1	5/4
Medial Frontal Gyrus		2/0		1/1		1/1	1/0	1/0		3/0	1/0	0/2	1/0			1/0	1/0	
Middle Frontal Gyrus	0/1	2/3	0/1	2/1		4/3	0/1	0/1	0/2	3/2	2/3	0/3	1/2	0/1			1/3	1/0
Inferior Frontal Gyrus	3/3	4/2		1/3	1/0		2/2	2/6	1/1	1/1	1/1	2/1	2/1	1/1	2/1	1/1	1/1	0/1
Paracentral Lobule		1/2	3/0		1/0					1/0						1/0		
Anterior Cingulate											0/1							
Cingulate Gyrus				0/1		0/1						0/1						
Posterior Cingulate					1/0							1/0					1/1	
Insula		3/0		1/0				1/0			1/0	1/0			0/1			
Postcentral Gyrus			1/1	1/0	1/4	1/2	1/2		0/2	3/0			1/0					0/4
Superior Parietal Lobule									1/0									
Inferior Parietal Lobule		1/0	1/0	1/0	1/1	0/1			2/0	1/0	1/0	0/2						0/5
Supramarginal Gyrus							0/1											
Precuneus	1/0	1/2		1/0	2/0				1/3	2/1	1/0	2/1	1/0				0/1	2/0
Superior Occipital Gyrus									1/0									
Middle Occipital Gyrus												0/4						
Inferior Occipital Gyrus			2/1	1/0									2/0				1/0	
Cuneus				0/1					3/3			2/0			0/1		1/2	
Lingual Gyrus				1/0					2/1			1/3						
Fusiform Gyrus			1/1	1/1			1/0		1/0	0/2							2/0	1/0
Superior Temporal Gyrus	7/4	5/5	7/6	8/3	4/3	5/4	4/6	6/6	3/5	7/7	6/9	4/5	6/6	6/5	4/3	3/3	6/6	6/2
Middle Temporal Gyrus		2/2	3/2	3/3	3/5	2/5	1/1	3/2	1/3	3/3	0/2	3/2	0/2	2/2	3/2	1/1	5/4	1/4
Inferior Temporal Gyrus			1/2		1/1			0/4			0/1				1/1		0/1	
Transverse Temporal Gyrus		0/1		0/1				0/1				0/1	1/0		1/0		0/1	1/1

Table 7.3: Principal activation denoted by number of foci for each participant (left/right) for the visual contrast

Anatomical Region	Healthy controls									Stroke patients								
	C1	C2	C3	C4	C5	C6	C7	C8	C9	P1	P2	P3	P4	P5	P6	P7	P8	P9
Precentral Gyrus	3/0		1/1	2/0	1/0	0/2	2/1	1/1			0/2		0/1		0/2	1/0		0/1
Superior Frontal Gyrus		0/1	1/0	1/3	3/1	0/1	9/3	0/5		1/2	1/4	3/1	6/6		1/1	4/1		2/5
Medial Frontal Gyrus					1/0		0/1	1/0		1/1	1/0		4/0			1/1		2/3
Middle Frontal Gyrus	0/1	2/0	1/0	0/6		1/2	6/6	3/3		2/3	6/5	0/3	4/4		9/3	4/5		2/3
Inferior Frontal Gyrus	0/3	2/0	0/2		3/1	3/2	3/3	2/2		3/2	4/2	0/1	2/4		2/1	1/2		1/3
Paracentral Lobule											2/0							1/1
Anterior Cingulate													1/2					
Cingulate Gyrus							0/1				3/1							
Posterior Cingulate							1/0				0/1							0/3
Insula			1/0				0/1			2/1	1/0				1/0			
Postcentral Gyrus	1/0		0/1		5/0	0/1	1/1	1/0		0/1	0/1	4/3	0/1		4/1			0/3
Superior Parietal Lobule	2/2		1/0				2/1	1/0	1/1	2/1		2/0	1/1			1/0		
Inferior Parietal Lobule						0/1	3/0	0/1		1/0	2/2	1/0	0/2					
Angular Gyrus																0/1		
Precuneus	1/0					0/3	1/1	0/2		1/1	3/2		2/1		0/1	0/1	1/0	0/3
Superior Occipital Gyrus																		2/0
Middle Occipital Gyrus	2/3	1/1	1/2	1/2	2/2	2/3	2/2	1/2	4/3	3/3	0/2	2/1	1/2	2/2	2/2	0/2	1/1	1/1
Inferior Occipital Gyrus	1/1	1/0	3/0			1/0	1/1	1/1	1/0	0/1	0/1	0/1	0/1	0/1	0/1		1/1	0/1
Cuneus	1/1	2/3	2/0	2/2	2/3	1/0	1/1	1/4	1/1		1/2	1/1	1/0	3/1		0/1	0/1	3/1
Lingual Gyrus		1/1	1/1	0/1	2/1		0/1	1/0	1/0	0/1	1/1	1/1	0/1	2/1	1/0	3/0	0/1	0/3
Fusiform Gyrus	2/2	2/1	0/1	0/1	3/1				1/1		0/1		1/0	1/1	0/1	0/1	1/0	2/2
Superior Temporal Gyrus					1/4	2/0	1/6	1/0	0/1	3/0	0/1	1/0	6/2	1/1	1/0	1/7		3/3
Middle Temporal Gyrus	2/1	1/1	0/1	0/1	1/1	1/2	1/1	1/1	1/0	1/0	0/1	0/1	6/0	0/1	1/5	0/4		2/3
Inferior Temporal Gyrus		0/1							1/0									0/1

Table 7.4: Principal activation denoted by number of foci for each participant (left/right) for the (bimodal) video contrast

Anatomical Region	Healthy controls									Stroke patients								
	C1	C2	C3	C4	C5	C6	C7	C8	C9	P1	P2	P3	P4	P5	P6	P7	P8	P9
Precentral Gyrus	1/0	1/0	2/6	3/1	5/3	3/1	1/1	2/3	2/1	2/1	1/2	4/0	3/2		1/1	2/0	5/2	2/1
Superior Frontal Gyrus	4/6	1/4	1/2	2/3	2/5	1/1	5/7	2/3	8/1	4/2	4/0	4/3	3/2		1/1	5/4	5/1	4/8
Medial Frontal Gyrus	4/2	1/0	2/1	3/2	1/1	2/1	1/1	4/5	2/0	1/0	2/0	1/6	2/3		1/1	1/0	1/0	
Middle Frontal Gyrus	1/5	0/4	0/1	1/3	2/3	3/4	0/1	2/1	1/1	1/3	1/4	1/2	1/2	1/3	6/0	1/2		2/1
Inferior Frontal Gyrus	1/3	3/4		2/4	2/4	1/3	2/0	3/2	1/1	2/4	1/3		3/0	1/0	4/0	1/1	1/0	0/1
Orbital Gyrus														0/2				
Paracentral Lobule			1/1		1/0	0/1		1/0		1/0		0/1	0/1		1/0			
Anterior Cingulate	1/1											1/0	1/1					
Cingulate Gyrus	2/0		2/3	1/1	1/0					1/1					2/2			
Posterior Cingulate					1/0		1/0		2/1	1/0								1/0
Insula					0/1		0/1								2/0			
Postcentral Gyrus	1/1		2/2	1/0	5/4	2/0	0/1	1/1			1/1	2/5			3/0			0/3
Superior Parietal Lobule	1/0	0/1			1/0		1/1	1/1	0/2		0/1	3/2			1/0		0/1	
Inferior Parietal Lobule	1/0	1/0		3/0	1/3				1/0	2/0	1/0	1/0			2/1			0/2
Angular Gyrus									1/0									
Precuneus		1/3	2/0		1/0	0/1	0/2	1/2	1/1	0/1	1/3	0/1		0/1	3/2	0/1	5/1	0/1
Middle Occipital Gyrus	1/0	1/3	0/1	0/2	0/3	1/3	2/1		1/1	2/2		0/1	1/1	2/1	1/0	0/2	0/1	0/1
Inferior Occipital Gyrus	2/0	1/0						1/1		0/1			0/1	0/1		2/1	1/0	1/1
Cuneus	1/0	1/1				1/0	1/0	0/1	1/0		1/0	0/1	0/1	3/0	1/0	0/1	0/1	2/1
Lingual Gyrus	1/0	0/1		0/1	1/0		0/1						0/1	3/0	1/0	1/0	0/1	0/2
Fusiform Gyrus	0/1	0/2					1/0		1/0				1/0	0/1	1/1			0/1
Superior Temporal Gyrus	2/3	4/3	2/4	3/4	4/2	0/1	3/2	2/2	3/1	5/3	5/4	2/2	1/1	3/2	3/2	8/8	2/3	5/3
Middle Temporal Gyrus	1/0	2/5	0/1	3/1	1/1	0/1		2/2	1/1		0/2	1/1	1/0	1/3	1/2	1/2		1/5
Inferior Temporal Gyrus	1/0	0/2						1/1	0/1				0/1	1/0			1/0	
Transverse Temporal Gyrus		0/1													1/0			1/1

7.3.3 Voxel-based Analysis

For each participant and contrast the number of activated voxels was computed separately for each hemisphere ($p<0.001$, uncorrected). Table 7.5 shows the mean percentage of activated voxels for each specific brain region of all healthy participants and stroke patients separately for all contrasts. These results reflect the findings from the foci analysis: a) The auditory contrast mainly activated temporal regions, frontal, and parietal areas. b) In the visual contrast we found mainly occipital areas which were activated, as well as (less) frontal activation, and minor temporal activation. Apart from that we found many activated voxels in the superior parietal lobule. c) The video contrast showed a mixture of the other two contrasts with activated voxels in temporal and occipital areas. Parietal and frontal areas showed more activated voxels than in the unimodal contrasts, except for the superior parietal lobule (both groups), the angular gyrus, and precuneus (stroke patients).

A one-sided paired t-test was conducted to test the number of activated voxels between both groups. Here, the exact number of activated voxels for each brain region was compared (not percentage of voxels). A trend was observed for the left inferior temporal gyrus ($p=0.092$) for the auditory contrast. Patients showed more activated voxels than healthy participants. Significant differences and trends were obtained for the left superior occipital gyrus ($p=0.096$), left inferior temporal gyrus ($p=0.089$), right postcentral gyrus ($p=0.089$), right inferior occipital gyrus ($p=0.057$), and right fusiform gyrus ($p=0.042$) for the visual contrast. In this contrast patients showed more activated voxels than healthy participants, except for the temporal gyrus. In the video contrast trends and significant differences were reported for the left precentral gyrus ($p=0.062$), the left precuneus ($p=0.058$), the left inferior temporal gyrus ($p=0.036$), the right angular gyrus (0.06), the right superior occipital gyrus ($p=0.051$), and right inferior temporal gyrus ($p=0.09$). All patients showed less activated voxels than healthy controls. Bonferroni correction for multiple t-tests was not applied, because of the low number of participants and high variability of activated voxels. This has to be kept in mind and the (anyway low significances) have to be interpreted with caution.

Table 7.5: Overview of activated voxels for all three computed contrasts:

Mean values (± standard deviation) of healthy controls and stroke patients for left and right hemisphere separately (in percentage of the specific brain region)

Contrast	Auditory vs. Rest				Visual vs. Rest				Video vs. Rest			
Hemisphere	Left		Right		Left		Right		Left		Right	
Anatomical region	Healthy	Stroke	Healthy	Stroke	Healthy	Stroke	Healthy	Stroke	Healthy	Stroke	Healthy	Stroke
Precentral Gyrus	1.06±0.74	1.06±0.96	0.93±0.44	1.30±1.15	0.37±0.62	0.37±0.51	0.27±0.29	0.52±0.74	1.81±0.90	1.22±0.60	1.58±0.89	1.42±1.00
Superior Frontal Gyrus	0.11±0.11	0.37±0.61	0.09±0.08	0.33±0.53	0.10±0.23	0.19±0.28	0.11±0.18	0.29±0.44	0.40±0.56	0.27±0.30	0.48±0.49	0.43±0.45
Medial Frontal Gyrus	0.16±0.14	0.22±0.46	0.07±0.09	0.17±0.29	0.03±0.07	0.16±0.43	0.01±0.03	0.10±0.26	0.43±0.44	0.31±0.55	0.51±0.58	0.27±0.39
Middle Frontal Gyrus	0.21±0.20	0.54±1.27	0.26±0.16	0.49±1.07	0.37±0.72	0.74±1.05	0.83±0.83	0.92±1.00	0.64±0.41	0.56±0.67	1.37±1.02	0.80±0.80
Inferior Frontal Gyrus	0.94±1.00	1.00±0.90	0.58±0.50	0.47±0.40	0.60±1.62	0.86±1.11	0.72±1.10	1.11±1.15	2.07±1.49	1.47±0.99	1.76±1.07	1.82±1.91
Paracentral Lobule	0.03±0.10	0.04±0.10	0.01±0.03	0.00±0.00	0.00±0.00	0.11±0.27	0.00±0.00	0.06±0.17	0.04±0.07	0.06±0.13	0.21±0.52	0.03±0.10
Postcentral Gyrus	0.98±0.87	1.29±1.06	1.02±0.66	1.29±1.15	0.09±0.15	0.11±0.18	0.04±0.07	0.31±0.52	1.44±0.92	1.36±0.51	1.33±0.76	1.17±0.67
Superior Parietal Lobule	0.00±0.00	0.82±2.47	0.01±0.03	0.51±1.53	1.50±2.25	1.38±2.22	1.99±2.40	2.08±3.33	1.40±1.97	0.73±1.41	2.36±2.87	1.00±2.45
Inferior Parietal Lobule	0.99±1.04	1.22±1.82	0.36±0.54	0.76±1.49	0.40±0.71	0.31±0.72	0.53±0.58	0.70±1.04	1.30±0.90	1.00±0.74	1.24±1.17	1.02±1.36
Supramarginal Gyrus	0.64±1.43	1.06±2.07	0.07±0.17	0.16±0.37	0.53±1.45	0.27±0.40	0.44±0.97	0.66±0.76	1.43±2.55	0.90±1.37	1.00±1.45	0.53±1.09
Angular Gyrus	0.00±0.00	0.34±1.03	0.00±0.00	0.17±0.50	0.04±0.10	0.21±0.49	0.40±0.68	0.42±0.84	0.17±0.32	0.12±0.27	0.63±0.98	0.07±0.20
Precuneus	0.11±0.16	0.50±1.35	0.03±0.07	0.40±0.98	1.04±1.33	0.76±1.11	1.47±1.83	1.53±1.72	1.72±1.84	0.58±0.85	2.22±2.16	1.06±1.47
Superior Occipital Gyrus	0.02±0.07	0.09±0.27	0.00±0.00	0.27±0.80	1.78±2.12	3.79±3.82	2.21±2.25	2.59±3.70	2.53±2.85	2.38±3.77	3.00±2.65	1.24±1.47
Middle Occipital Gyrus	0.02±0.07	0.02±0.04	0.00±0.00	0.09±0.27	7.99±2.31	8.20±2.41	8.19±1.71	8.34±1.58	8.36±2.76	7.46±2.91	8.44±2.30	7.19±2.09
Inferior Occipital Gyrus	0.82±2.36	0.07±0.20	0.03±0.10	0.00±0.00	10.73±3.22	10.03±3.04	8.90±2.15	10.50±1.82	10.98±3.36	9.51±3.13	9.24±2.85	9.82±2.57
Cuneus	0.66±1.97	0.04±0.10	0.17±0.50	0.02±0.04	3.89±3.24	4.72±2.99	4.64±2.94	6.06±3.48	5.02±3.35	3.93±2.55	6.09±3.35	5.16±3.16
Lingual Gyrus	0.61±1.65	0.02±0.07	0.11±0.30	0.02±0.07	6.18±3.36	6.08±2.88	6.69±3.18	8.04±2.95	7.36±3.62	6.37±4.08	8.08±3.83	7.86±3.18
Fusiform Gyrus	0.22±0.45	0.07±0.11	0.01±0.03	0.20±0.60	4.57±1.80	5.18±2.15	5.51±1.67	6.81±1.34	6.13±2.21	4.98±1.61	6.53±2.10	6.81±1.35
Superior Temporal Gyrus	6.43±1.39	7.17±1.71	5.93±1.62	6.74±1.66	1.01±1.41	0.98±1.25	1.34±1.31	1.86±1.05	7.60±1.63	8.14±1.73	7.49±2.21	8.26±1.97
Middle Temporal Gyrus	2.91±1.03	2.97±1.46	2.92±0.98	3.24±0.93	1.88±0.92	2.27±1.40	2.68±1.06	2.84±1.16	5.90±1.21	5.24±2.27	6.57±1.50	6.10±1.82
Inferior Temporal Gyrus	0.10±0.16	0.31±0.38	0.29±0.46	0.20±0.21	1.67±0.36	1.46±0.33	2.07±0.77	1.74±0.38	2.08±0.66	1.54±0.46	2.47±0.88	1.92±0.69
Transverse Temporal Gyrus	11.32±2.13	11.63±2.59	9.96±1.94	10.77±2.04	0.00±0.00	0.12±0.30	0.00±0.00	0.00±0.00	11.12±2.50	11.71±2.74	9.76±2.07	10.22±2.27
Insula	2.01±1.40	2.27±1.12	1.78±1.37	2.12±1.51	0.16±0.47	0.03±0.10	0.17±0.33	0.08±0.13	1.82±1.38	1.97±1.01	1.98±1.67	1.89±1.23

The mean percentage of activated voxels for all four lobes of the auditory contrast for all participants is shown in Figure 7.3. For simplification fusiform and lingual gyri were included in the occipital lobe and the insula was included in the temporal lobe. The temporal lobe showed the highest percentage of activated voxels. Amusic patient P2 presented a high number of activated voxels for the frontal and parietal lobes. Therefore frontal and parietal lobes were inspected in detail with respect to P2 compared to all other participants. For the other two contrasts no such 'peculiarities' were found. Subcortical regions showed activation in some participants as well, but these were major activations in only two participants, a few others showed minor (below 1%) activation.

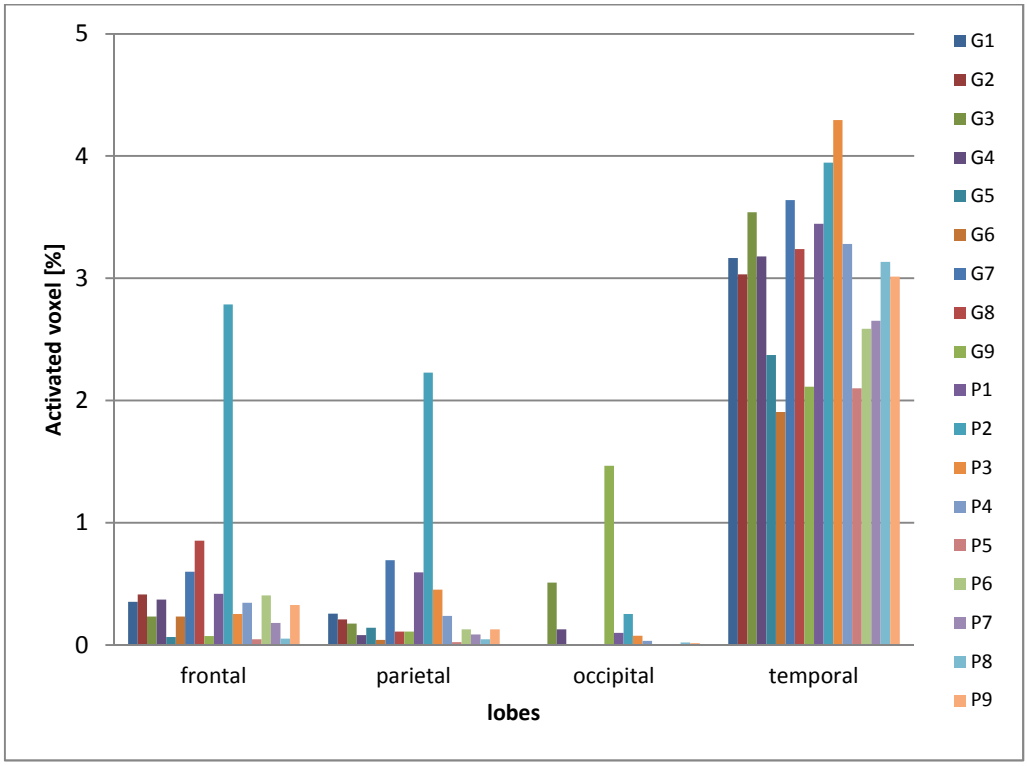

Figure 7.3: Percentage of activated voxels for all four lobes for both hemispheres (contrast: auditory vs. rest), C1-9 denote results for healthy control participants and P1-9 the results for the stroke patients.

7.3.4 Amusic Patient P2

The number of activated voxels for frontal and parietal regions can be seen in Figures 7.4 (left hemisphere) and 7.5 (right hemisphere). In several brain regions patient P2 presented a high number of activated voxels compared to all other participants. P2 was the only participant with activation in the left superior parietal lobule, only one other participant also showed minor activation for the right superior parietal lobule. Additionally P2 had major activation in the right angular gyrus. In contrast to these findings P3 (chronic amusia patient) showed major activation in the left angular gyrus. All other brain regions were compared with the method established by Crawford and colleagues (Crawford & Garthwaite, 2002; Crawford & Howell, 1998). The exact number of

activated voxels for each brain region in each hemisphere of P2 was compared to the group of other participants: a) only the stroke patients, b) only the healthy participants, c) all healthy participants and stroke patients combined. Highly significant differences were obtained for the precentral gyrus, superior, medial and middle frontal gyri, inferior parietal lobule, and precuneus ($p<0.01$). For the postcentral gyrus all differences were highly significant ($p<0.01$), except for the comparison of P2 to healthy controls ($p=0.013$). Only the left supramarginal gyrus showed significant differences between P2 and the three different groups ($p<0.05$).

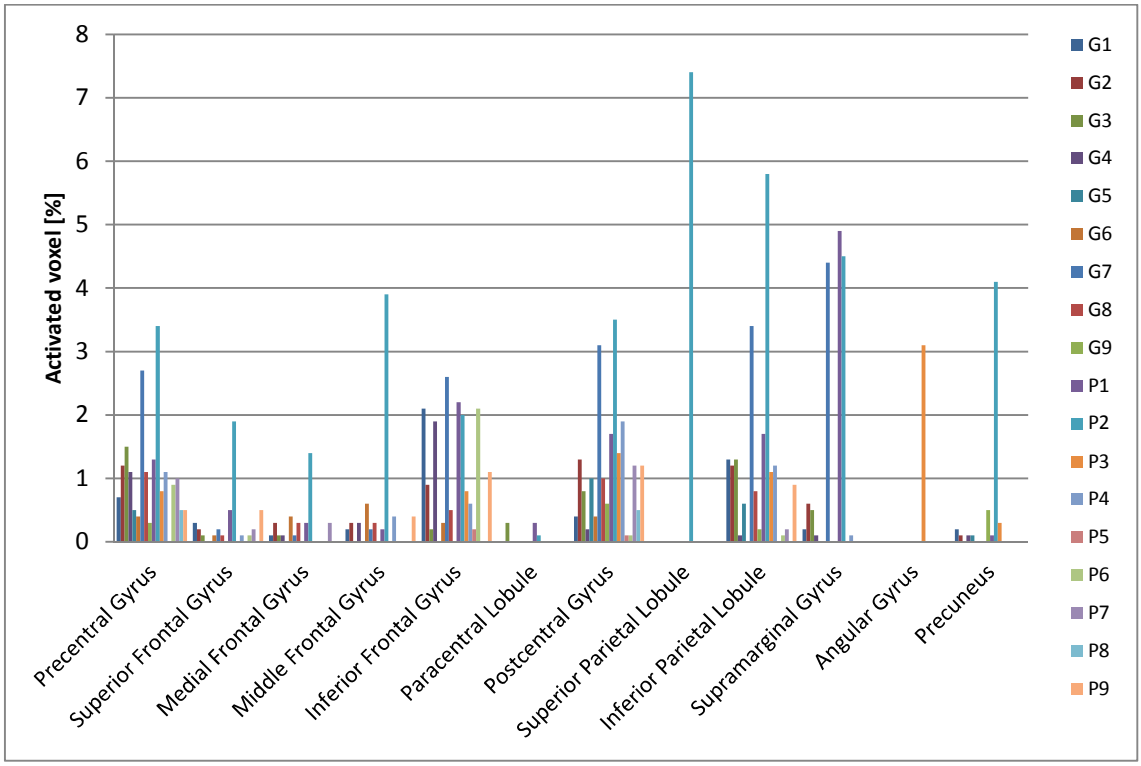

Figure 7.4: Percentage of activated voxels for left frontal and parietal regions (contrast: auditory vs. rest), C1-9 denote results for healthy control participants and P1-9 the results for the stroke patients.

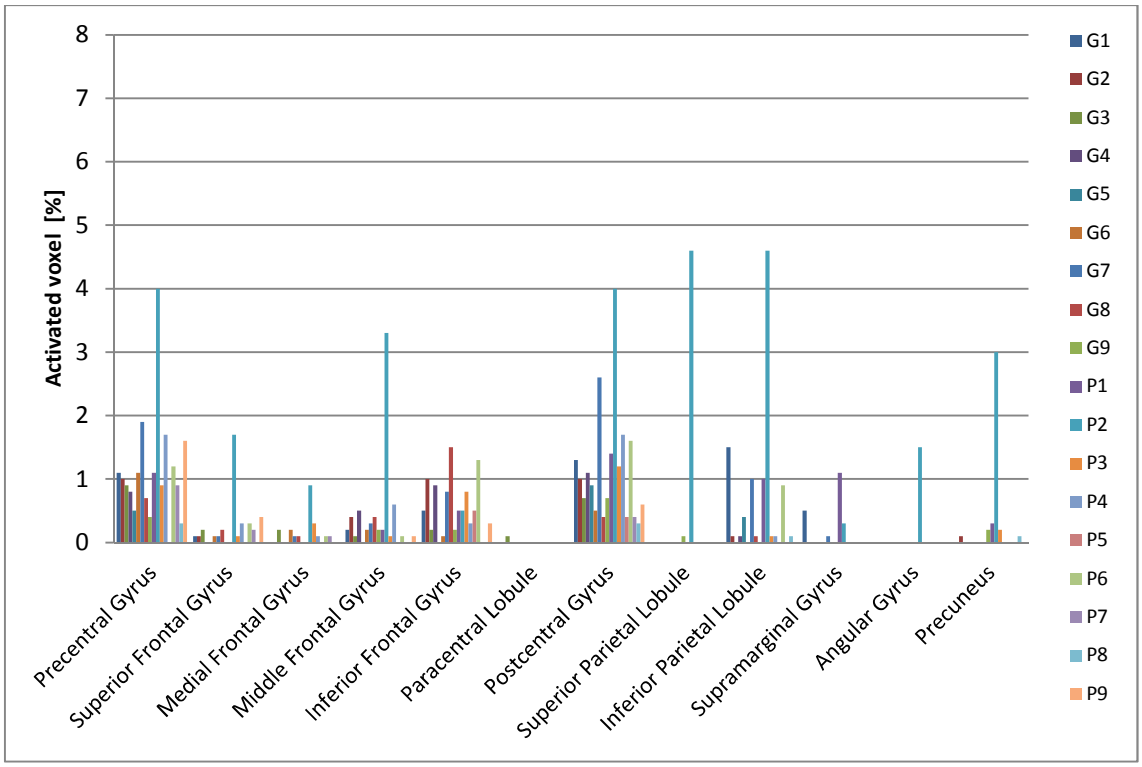

Figure 7.5: Percentage of activated voxels for right frontal and parietal regions (contrast: auditory vs. rest), C1-9 denote results for healthy control participants and P1-9 the results for the stroke patients.

The insula was inspected for abnormal brain activation as well, because of its role in the music perception network pointed out in the literature. Significant differences were obtained for the comparison of Patient P2 with a) other stroke patients ($p=0.031$) and c) all healthy participants and stroke patients ($p=0.048$). The comparison of P2 with healthy participants (b) yielded a trend ($p=0.092$).

Patient P2 took part in a re-test of behavior and imaging six months after his stroke. Compared to the initial measurement, he improved in both MBEA tasks: he achieved 100% in the melody perception and 86% (26 correct answers) in the rhythm perception task. Both scores are well above the cut-off score for amusia. Evaluation of number of activated voxels showed a decrease (from initial to the re-test measurement) in almost all brain areas (Figure 7.6, Fable 7.6). However, damage of the basal ganglia was still visible on the T1 and T2 images after six months.

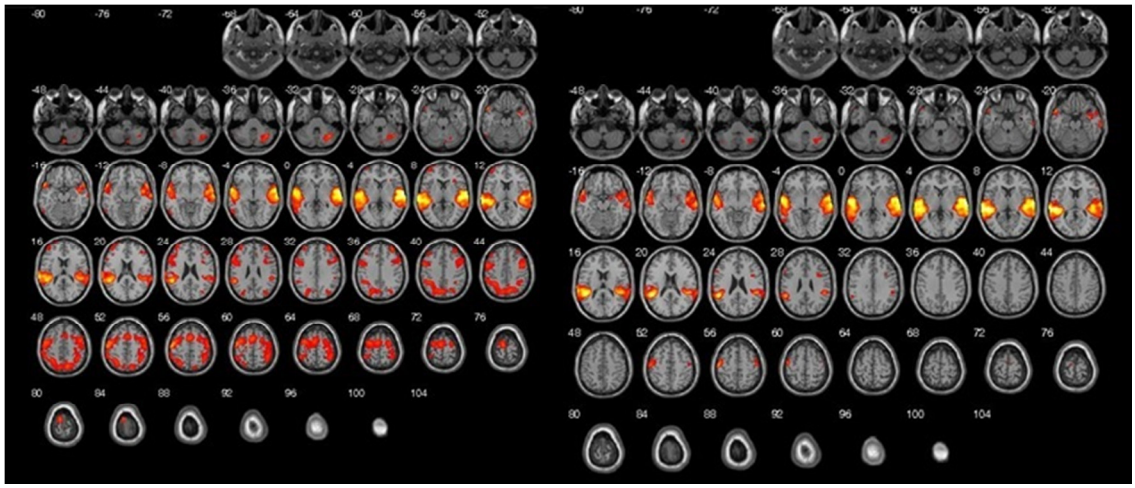

Figure 7.6: Axial slice view of the auditory contrast activation in Patient P2 for two measurements (left: subacute, right: chronic).

Table 7.6: Mean number of activated voxels for patient P2 at subacute and chronic stage, P3 (only chronic) and all other participants (mean of healthy and all other stroke patients)

	P2 subacute	P2 chronic	P3	Mean of all other participants
Precentral Gyrus	2.47	0.67	0.57	0.63
Superior Frontal Gyrus	7.07	0.00	0.03	0.26
Medial Frontal Gyrus	1.17	0.00	0.10	0.07
Middle Frontal Gyrus	2.40	0.07	0.03	0.13
Inferior Frontal Gyrus	0.83	0.07	0.53	0.48
Paracentral Lobule	0.03	0.00	0.00	0.01
Postcentral Gyrus	2.50	0.60	0.87	0.65
Superior Parietal Lobule	4.00	0.00	0.00	0.00
Inferior Parietal Lobule	3.47	1.17	0.40	0.38
Supramarginal Gyrus	1.60	1.27	0.00	0.26
Angular Gyrus	0.50	0.00	1.03	0.00
Precuneus	3.50	0.00	0.87	0.04
Superior Occipital Gyrus	1.07	0.00	0.00	0.00
Middle Occipital Gyrus	0.03	0.00	0.27	0.01
Inferior Occipital Gyrus	0.00	0.00	0.00	0.17
Cuneus	0.40	0.00	0.07	0.36
Lingual Gyrus	0.00	0.00	0.13	0.23
Fusiform Gyrus	0.03	0.00	0.00	0.09
Superior Temporal Gyrus	5.90	5.87	5.80	4.20
Middle Temporal Gyrus	2.17	3.03	3.63	1.90
Inferior Temporal Gyrus	0.37	0.03	0.37	0.12
Transverse Temporal Gyrus	8.67	8.67	8.70	7.10
Insula	2.63	2.33	2.97	1.18

The obtained values were compared to patient P3 (amusia patient measured three months after the stroke) and all other participants without amusia. The high amount of activated

voxels in frontal gyri of P2 almost disappeared. The number of activated voxels in pre- and postcentral gyri dropped to nearly the mean number of all other participants and was comparable to P3. The same holds true for the superior parietal lobule, precuneus, and angular gyrus. The number of activated voxels in the inferior parietal lobule and supramarginal gyrus decreased as well but were still much higher than in P3 or the mean of all other participants. Activation in the insula was equally high for both amusic patients and for both measurements in P2. All values were higher than the mean of all other participants.

7.4 Discussion

This study was carried out with two evident previous findings in mind: 1) Brain areas associated with music processing in healthy participants and brain lesions inducing amusia symptoms are not always consistent across the literature and 2) no study has explored functional correlates of amusia so far. Hence, we wanted to investigate the impact of a focal brain lesion leading to amusia symptoms on other brain areas supposed to process musical input.

Here, we report two cases of amusia: one with a basal ganglia lesion and a deficit in rhythm perception (P2) and one with frontal lobe lesion and impairment both in melody and rhythm perception (P3). First, general results will be discussed, then the differences between healthy controls and stroke patients. Finally and in more detail, the findings of the two amusia patients compared with the other participants will be discussed.

7.4.1 General Activation Pattern

In this study three different contrasts were computed: auditory stimulation vs. rest, visual stimulation vs. rest, and bimodal auditory and visual stimulation (video) versus rest. Stimulation sequences consisted of a German musical song. Individual data analysis of foci and number of voxels revealed a main activation pattern in temporal, frontal, and parietal areas for the auditory contrast. In the visual contrast brain areas in occipital and frontal regions were recruited and the superior parietal lobule showed many activated voxels. The bimodal auditory and visual contrast presented a combination of the other two contrasts: Many activated voxels in temporal and occipital regions were found. Besides, parietal and frontal areas showed more activated voxels than in unimodal contrasts, except for the superior parietal lobule, angular gyrus, and precuneus. These results very well reproduce findings from the literature. Temporal and occipital regions are involved in the processing of auditory and visual stimuli. Additionally our stimulation invoked recruitment of frontal and parietal areas. As our stimulus was a German musical song,

melody, rhythm, beat, and speech had to be processed and the whole network for music processing was activated. Frontal and parietal areas may have processed melody and pitch (Foster & Zatorre, 2009; García-Casares et al., 2013; Koelsch, 2011; Lee et al., 2011; Schwenzer & Mathiak, 2011). Premotor and supplementary motor areas may have engaged in beat perception (Fedorenko et al., 2012; Grahn & Brett, 2009; Zatorre et al., 2007) and rhythm perception may be achieved by frontal, parietal, and temporal regions (Thaut et al., 2014). It is possible that the wide distribution of activation is not only or maybe not at all connected to the perception of the presented music per se. As frontal and parietal areas were also activated during visual and bimodal stimulation the increased BOLD signal could be correlated to the participants' strategy during the task: although it was a passive listening task, the presentation was in chronological order of the song and the singers were acting at the same time (musical). Therefore, keeping track of the storyline as well as evaluating the behavior of the performers could have happened during the stimulation as well. A recent study evaluating attentive listening to music showed that areas in frontal, parietal, and temporal cortices engage in this task, a network associated with domain-related attention and working memory (Janata et al., 2002). A comparison of our results for the different contrasts showed that a few regions were not equally activated throughout the whole experiment: Pre- and postcentral gyri were more activated during auditory and bimodal stimulation while the superior parietal lobule and precuneus were mainly activated during visual and bimodal presentation. These findings are partly supported by the foci based analysis. More participants showed principal activation in precentral gyrus for the auditory and video contrast (up to 100%) compared to the visual contrast (up to 67%). Foci in the postcentral gyrus were visible in all three contrasts. Principal activation in superior parietal lobule and precuneus was observed more often in contrasts two and three (up to 89%) compared to contrast one (up to 56%). Hence, we argue from the general activation pattern we observed across all participants that pre- and postcentral gyri seem to be important for processing the musical input in our stimuli and that superior parietal lobule and precuneus seem to play a role for the perception of the visual input of our stimuli.

7.4.2 Stroke Patients compared to healthy controls

For the three computed contrasts foci and number of activated voxels for all participants and stroke patients were extracted and then compared across groups by Chi^2- and T-statistics. Fewer patients showed at least one focus in precentral and postcentral gyri, left inferior occipital gyrus, cuneus, and medial frontal gyrus compared to healthy participants. More patients had at least one focus in right inferior occipital gyrus and medial frontal gyrus. This was partly reflected by the T-statistics comparing the number of

foci across groups. The voxel based analysis showed that patients tended to show more activated voxels in temporal, occipital, fusiform, and postcentral gyri, for the unimodal conditions. On the other hand activated voxels in temporal, precentral, angular, and occipital gyri, additional to the precuneus for the bimodal contrast seemed to be fewer in patients (keep in mind: no Bonferroni-correction).

Patients show a more widely distributed activation pattern (more activated voxels) which is less focused (fewer foci) than healthy participants for the unimodal contrasts compared to the bimodal contrast. This could be due to compensatory mechanisms (Calautti et al., 2001a; Feydy et al., 2002; Grefkes et al., 2007; Marshall et al., 2000; Meehan et al., 2011; Ward et al., 2003) or global brain function changes in areas connected with or close to the lesion (de Haan, Rorden & Karnath, 2013; Gratton et al., 2012). Five of our nine patients presented behavioral deficits in either musical or visual perception. Higher activation was found only for unimodal conditions and was present in temporal, occipital, fusiform, and postcentral gyri. None of the patients presented lesions in these areas. On the other hand the bimodal stimulation contrasted to rest showed a fewer number of activated voxels in temporal, precentral, occipital, and parietal areas in patients compared to controls. These areas correspond better to the lesions of the patients, except for the occipital regions. That means, we found lower activation in damaged and nearby regions for bimodal stimulation but higher activation in areas needed to process exclusively unimodal stimuli. Hence, we argue that the increased BOLD signal found for the unimodal stimulation is a compensatory mechanism. It could be possible that it is only needed when the specific modality is presented alone. If the input is bimodal the unaffected modality may take over the processing of the input (at least partly) and no compensation would be needed.

7.4.3 Correlates of Amusia

Amusia patient P2 was of particular interest in this study because he presented acute amusia symptoms, participated in the fMRI experiment ten days after stroke and was re-tested after six months.

In several brain regions patient P2 presented more activated voxels compared to all other healthy participants and patients. Significantly more activated voxels were obtained for precentral gyrus, superior, medial and middle frontal gyri, inferior parietal lobule, left supramarginal gyrus, and precuneus. Only P2 showed high activation in the superior parietal lobule, whereas all other participants did not show any activation in this area. Comparing these results with the re-test six months later one can see that the high amount of activated voxels in frontal and parietal gyri dropped in P2, mostly to zero (or close to zero) or close to the mean of the other participants. Activated voxels in the inferior

parietal lobule and supramarginal gyrus decreased as well but are still much higher than in P3 or the other participants. Insula activation was high for both amusia patients for both time points and higher than for the other stroke patients or healthy participants. Hence, we found a network of frontal and parietal areas showing 'overactivation' in the subacute amusia stage but not in the chronic/recovered stage or in any other participants. The behavioral deficit was gone after six months as well. Hence, we have two possible explanations: compensatory mechanisms or changes of global brain function. Studies investigating hemiparetic patients found greater and more widespread activation in early compared to late stages after stroke, suggesting compensatory mechanisms which decrease when motor functions recover (Calautti et al., 2001a; Feydy et al., 2002; Grefkes et al., 2007; Marshall et al., 2000; Meehan et al., 2011; Ward et al., 2003). Another study found abnormal perfusion in the superior temporal gyrus, intraparietal lobule, and inferior frontal gyrus after basal ganglia stroke (Karnath et al., 2005). Premotor cortex and supplementary motor area are connected to the basal ganglia (Ward et al., 2003). Hence, the increased BOLD signal we observed could be due to a disturbed connection between basal ganglia and fronto-parietal cortical areas. An argument against this explanation could be that the increased signal was only obtained for the unimodal stimulation and not for the bimodal stimulation. If the same processes are engaged for any musical input (either uni- or bimodal), the same effect would have been found for the bimodal contrast as well. Hence, we are again arguing for compensatory mechanisms which are present when only the affected modality is stimulated. Support for this idea could be the fact that the perception of irregular chords activates inferior frontal and orbito-frontal gyri, insula, premotor and temporal cortices, and the supramarginal gyrus (Koelsch et al., 2005). Possibly, P2 is experiencing the auditory stimulation as an unpleasant or strange sound (due to his amusic symptoms) and therefore has the same experience as healthy participants present when hearing irregular chords.

Critical regions seem to be the inferior parietal lobule and supramarginal gyrus as their activation was still increased in Patient P2 in the recovered state after the initial stroke. In other studies the perception of rhythm was characterized by activation in supramarginal gyrus, postcentral gyrus, and right precuneus (Thaut et al., 2014). In line with these findings is the report of an amusia patient with lesions in the inferior parietal lobule presenting impaired discrimination of rhythms (DiPietro et al., 2004). As we do not see a behavioral deficit in P2 after six months but increased activation in these areas, one might come to the conclusion that these areas try to compensate for the initial damage to basal ganglia and the impairment in rhythm perception. The fact that the behavioral deficit diminished but the damage of basal ganglia is still visible yields the conclusion that the

compensation actually worked very well. This suggestion would also fit into the network-idea where global changes in connected brain areas result from focal brain damage (Gratton et al., 2012). The insula seems to be connected to amusia per se, as a high activation was found for both patients at both investigations and is not necessarily connected to recovering of musical functions. Patients P2 showed good musical abilities six months after the stroke but insula activation was still high. It could be the case that listening to music still evokes a strange feeling for the patients, like listening to irregular chords (Koelsch et al., 2005), although musical abilities started to recover and distinguishing between melodies was already possible.

7.4.4 Conclusion

Lesions of both amusia patients perfectly fit the music perception network already identified in the literature (García-Casares et al., 2013; Grahn & Brett, 2009; Koelsch, 2011; Merchant et al., 2008; Schwartze et al., 2011; Stewart et al., 2006). The impact of amusia on this network has not been investigated by fMRI so far.

From the general activation pattern we observed across all participants we supposed that pre- and postcentral gyri seem to be important for the perception of the musical input in our stimuli. All other frontal and parietal areas were activated for visual and bimodal input as well and we cannot exclude that these areas also subserve domain-general functions like working memory or attention. Comparing stroke patients with healthy participants we found increased activation in temporal, occipital, and postcentral regions for unimodal stimulation. We think that the recruitment of these additional areas is due to compensatory mechanisms after the stroke only needed for unimodal visual or musical stimulation but not for bimodal stimulation. Regarding results from amusia patient P2 in detail, we are again arguing for compensatory mechanisms. Our results demonstrate a larger and quite distributed activation in frontal and parietal areas for acute amusia. These BOLD signal increases were present in both hemispheres after a unilateral basal ganglia lesion. In the chronic amusia patient with frontal lobe lesion this ‘overactivation’ was not visible.

In summary, our results show distributed patterns of activation for musical input for healthy participants. In the amusic patient this activation was increased in frontal and parietal areas in the subacute phase. Parietal areas, specifically inferior parietal lobule and supramarginal gyrus, seem to play an important role in recovered amusia with rhythm perception deficit as they may take over processing tasks usually accomplished by intact basal ganglia. Activation in the insula seems to be connected to acquired amusia in general.

Although we are presenting arguments for compensatory mechanisms, no final differentiation between the two possible explanations (disturbed connection between basal ganglia and fronto-parietal areas or compensation in fronto-parietal areas) can be drawn unless further amusia patients are investigated with fMRI.

7.4.5 Limitations

The results presented in this study do not cover the whole complexity of music processing in general nor can the conclusions be applied to all amusia patients. Because of the small sample size, results should be interpreted with caution.

We screened 25 participants for music perception deficits and identified only two amusic patients. These two were invited for the imaging experiment and all other patients who were able and willing to participate in the experiment. The lesion overlap in our sample size was small and the variability in lesion size was large. However, the heterogeneity of the group permitted us to compare amusic patients with a variety of other patients to look for reasons for different brain activity and behavior. In our study we could rule out that our findings result from a) having a stroke in general, b) having a stroke with any behavioral deficits, and c) from chronic amusic symptoms. Differences between patients could be due to demographic or clinical values we did not access. Hence, definitely more studies are needed with lesions in similar brain regions to make any further assumptions about the effect of amusia on other brain areas and to rule out the possibility that the effects we find for P2 just result from basal ganglia infarctions in general and are not connected to amusia or music processing at all.

Although we present data from only one individual measured in the subacute stage, results are in line with previous investigations in healthy participants. This study strengthens the evidence that basal ganglia are involved in rhythm perception and that frontal and parietal areas play a major role in music perception.

8. Lateralization of music perception in healthy elderly people – an fMRI study

Stephanie Rosemann, Peter Erhard, & Manfred Fahle

Submitted to *Music Perception*

Abstract

Music perception is accomplished by a network of temporal, parietal and frontal areas. While most of these areas were identified by investigating young healthy subjects with fMRI, some of the areas were determined based on case studies with amusia patients (elderly stroke patients). But these areas do not always match. Aging is usually accompanied by changes in brain activation in temporal, parietal and frontal areas which are the important brain regions for music perception. Therefore an exploration of healthy elderly music perception seems to be required. In this study we explored music perception in twenty healthy individuals to compare their activation patterns with that of young participants reported in the literature. Additionally, we investigated individual voxel-based results and the contribution of different lobes and both hemispheres. As expected brain activation in response to musical stimulation versus rest was obtained in temporal, frontal and parietal regions. Temporal activation was highest, followed by frontal and parietal activation. Pre- and postcentral gyri, besides temporal gyri, showed robust activation in every participant. Highest contribution to the perception of music was seen in left lateralized precentral, inferior frontal, postcentral, superior and transverse temporal gyri, and the inferior parietal lobule. Hence, we find increased lateralization and a high engagement of frontal areas in healthy elderly participants.

8.1 Introduction

The perception of music is based on a widely distributed network of temporal, frontal, parietal, and subcortical structures (Alossa & Castelli, 2009; Peretz & Coltheart, 2003; Schuppert, Münte, Wieringa & Altenmüller, 2000). Investigations with functional magnetic resonance imaging (fMRI) in healthy subjects showed that different sub-functions of music perception are executed in distinct regions of the brain and a model of music perception has been developed (Clark, Golden, & Warren, 2015; García-Casares, Berthier Torres, Froudist Walsh, & González-Santos, 2013; Koelsch, 2011; Stewart, von Kriegstein, Warren, & Griffiths, 2006). These sub-functions can be involved in e.g. melody or rhythm perception, but they can also engage in processing of smaller elements like pitch and contour (Foster & Zatorre, 2009; Lee, Janata, Frost, Hanke, & Granger, 2011; Schwenzer & Mathiak, 2011; Stewart, Overath, Warren, Foxton, & Griffiths, 2008) or beat (Fedorenko, McDermott, Norman-Haignere, & Kanwisher, 2012; Grahn & Brett, 2009; Thaut, Trimarchi, & Parsons, 2014; Zatorre, Chen, & Penhune, 2007). An important finding is that melodic and rhythmic processing streams are dissociated in the brain (DiPietro et al., 2004; Griffiths, 1997; Jerde, Childs, Handy, Nagode, & Pardo, 2011; Peretz, 1990; Schuppert et al., 2000; Vignolo, 2003).

The network executing melodic information includes premotor cortex, prefrontal cortex, superior frontal gyrus, inferior frontal gyrus, intraparietal sulcus, inferior parietal lobule as well as temporal cortices (Fedorenko, McDermott, Norman-Haignere, & Kanwisher, 2012; Foster & Zatorre, 2009; Koelsch, 2011; Lee et al., 2011; Platel et al., 1997; Schwenzer & Mathiak, 2011). Temporal information is processed in superior temporal cortices, cerebellum, basal ganglia, premotor, and supplementary motor areas, supramarginal gyrus, and middle frontal gyrus (Bengtsson et al., 20009; Fedorenko et al., 2012; Grahn & Brett, 2009; Koelsch, 2011; Thaut, Trimarchi, & Parsons, 2014; Toiviainen, Alluri, Brattico, Wallentin, & Vuust, 2014; Zatorre, Chen, & Penhune, 2007). The insula is concerned with emotional music perception and processing of musical meaning (Bamiou, Musiek, & Luxon, 2003; LaCroix, Diaz, & Rogalsky, 2015; Thaut et al., 2014). Passive listening to music recruits bilateral and lateralized brain regions including frontal areas (inferior and medial frontal gyri), insula, pre- and postcentral gyri, and inferior parietal lobule, apart from temporal regions (LaCroix, Diaz, & Rogalsky, 2015). On the other hand, attentive listening to music engages a network of frontal, temporal, and parietal regions. Apart from music processing, this network is usually involved in domain-generalized attention and working memory (Janata, Tillmann, & Bharucha, 2002).

Damage to this music perception network can lead to a disorder known as amusia. Reported cases presented lesions in superior and middle temporal gyri, the insula, inferior parietal lobule or frontal areas (Ayotte, Peretz, Rousseau, Bard, & Bojanowski, 2000; Botez & Wertheim, 1959; DiPietro et al., 2004; Eustache, Lechevalier, Viader, & Lambert, 1990; Griffiths, 1997; Hochman & Abrams, 2014; Johkura, Matsumoto, Hasegawa, & Kuroiwa, 1998; Liegéois-Chauvel, Peretz, Babaï, Laguitton, & Chauvel, 1998; Mendez & Geehan, 1988; Patel, Peretz, Tramo, & Labreque, 1998; Peretz et al., 1994; Piccirilli et al., 2000; Satoh et al., 2005; Steinke, Cuddy, & Jakobson, 2001).

When comparing regions belonging to the healthy music perception network and reported lesions, one can notice that these areas do not always match. One reason for this discrepancy may be that the model for music processing has been developed for young healthy people, but stroke patients are usually older (above 40 years). Therefore, the question arises whether older people recruit other or more/less areas for the processing of musical input than young people do. If this is the case the model for music perception has to be broadened for older populations and the list of cerebral regions leading to amusia when damaged has to be extended.

Previous research on aging – not specifically concerned with music perception – identified brain regions which present less activity (temporal areas) or 'over-recruitment' (frontal and parietal areas) in older subjects compared to young controls. Other studies found a decreased lateralization in prefrontal areas in older participants (Cabeza, 2002). This increased activation can be compensatory or a sign of inefficiency and is usually seen in memory but also perceptual tasks (Grady, 2008). Especially in networks of brain regions effects of aging, namely reduced function or efficiency of the network, or compensatory recruitment of additional brain regions, were highlighted (Cabeza, 2002; Grady, 2008). Age-related structural and vascular changes may contribute to differences obtained in fMRI studies, but the full extent remains to be determined (Grady, 2012; Raz, 2000).

As aging effects are usually seen in temporal, frontal, and parietal areas, and these areas are involved in processing musical input, it seems to be of interest to explore the music perception network in healthy elderly people. Specifically, the aim of the present study was to determine if older adults present a similar or a different pattern of activation for music perception than young people. First attempts to compare music processing in young and older volunteers were conducted by Sikka and colleagues (2015). They compared the recognition of familiar melodies in young versus older healthy participants and found higher activation in the left superior temporal gyrus for young participants and higher activation in left superior frontal, left angular, and bilateral superior parietal regions for

older adults. To our best knowledge, no other study has explored music perception in healthy elderly people so far.

In contrast to the study by Sikka and colleagues in which an active memory task was required we focused on the question whether or not already passive listening to music engages other cortical regions in the elderly population than in young people. We present an exploratory study and describe the brain activation obtained during the holistic perception of the musical stimulus comparable to everyday music listening without any further demands in attention and working memory. The obtained activation pattern was compared to brain regions found for music processing in a younger sample presented in the literature (LaCroix, Diaz, & Rogalsky, 2015).

Based on previous work we hypothesized to find many different activated regions in temporal, frontal, and parietal areas. We expected bilateral activation in superior, middle and transverse temporal gyri, the medial frontal gyrus, insula, pre- and postcentral gyri, and inferior parietal lobule, and left-lateralized inferior frontal activation in response to a passive viewing task (LaCroix, Diaz, & Rogalsky, 2015). Apart from that we hypothesized to find a decreased lateralization in older adults (Cabeza, 2002) and increased recruitment of frontal and parietal areas (Grady, 2008; Sikka, Cuddy, Johnsrude, & Vanstone, 2015).

8.2 Material and Methods

8.2.1 Ethical Approval

This study was approved by the local ethics committee of the University of Bremen. Participants were informed about the aim and procedure of the experiment and had to sign a written consent form according to the Declaration of Helsinki. They were free to withdraw from the study at any time and they were paid for participation.

8.2.2 Participants

Twenty healthy people within the age range of 47 to 73 years and a mean age of 58.1 (±8.6) years participated in this study. All participants were native German speakers and right-handed. Exclusion criteria for participants were previous neurological, psychiatric or ophthalmological disorders, and auditory defects.

8.2.3 Stimuli

Stimuli consisted of twenty-four stimulation sequences taken from a German Musical song (Musical Elisabeth, Song: ‘So wie du’; DVD Live aus dem Theater an der Wien, 2005). Six video sequences were taken from this song and each was presented four times (four conditions): unimodal visual presentation, unimodal auditory presentation, bimodal

synchronous visual and auditory presentation, and bimodal asynchronous visual and auditory presentation with the visual being 560ms ahead of the auditory presentation. Only unimodal auditory stimulation is evaluated here.

For the presentation of auditory stimuli participants wore MR compatible headphones (CONFON HP-SC 02, MR confon GmbH, Germany) for the whole measurement session. Contact with the participant was possible via the headphones as well. Visual stimuli were presented by a projector (DLA-G15E, JVC Professional, Japan) retrofitted with a custom lens on a screen which was positioned behind the scanner at a distance of 140cm from eye to screen. Participants were able to look at this screen via a mirror which was attached to the head coil. Image size for visual stimulation was adjusted to 9.72° x 6.92° of visual angle and the videos were presented centrally.

A fixation dot was presented on grey background during auditory only presentation (green fixation point) and during the rest condition (red fixation point). Participants were instructed to fixate on the fixation point whenever it was present (rest and auditory condition) and to freely watch visual stimuli (video sequences). The participants lay in the scanner with lights off and no response or interaction was expected.

8.2.4 Data Acquisition

We used a 3T whole-body Siemens Magnetom Skyra MRI machine with a 20 channel receive only head coil for scanning. All participants conducted one functional run, a T1-weighted anatomical scan and a T2-weighted anatomical scan in one session (approximately 30 minutes scanning time). Functional images were acquired using an interleaved and ascending echo-planar imaging (EPI) sequence (TR = 2500 ms, TE = 30 ms, flip angle = 83°, slice thickness 3mm, 46 slices, 192x192 mm2). Structural images were acquired with a 3-D T1-weighted sequence (MP-RAGE, TR = 1900, TE = 2.07, flip angle = 9°, slice thickness 1mm, 176 sagittal slices). The T2-weighted images were collected to screen for structural abnormalities in the participants (TR = 4280 ms, TE = 9.4 ms, flip angle = 120°, slice thickness 3mm, 40 slices).

8.2.5 Experimental Procedure

Each participant performed one functional run of twelve minutes. The run consisted of twenty-four stimulation sequences (consisting of different conditions) with a duration of 20 seconds each, presented alternating with a 10 second resting condition. Before the experiment the participants completed a practice trial in which all conditions were presented by sequences taken from another song from the same Musical. The practice trial lasted for one minute (4 times 10 seconds stimulation and 4 times 5 seconds rest condition).

We used an eye-tracking system to control fixation and eye movements of the participants. One eye was recorded via the mirror above the participant's head during the whole measurement. Eye tracking data acquisition and stimuli presentation was achieved by in-house software based on Matlab (Matlab 2013a, The MathWorks, Inc., USA).

8.2.6 Data Analysis

The Statistical Parametric Mapping software package (SPM8, Welcome Department of Imaging Neuroscience, London, UK) based on Matlab served to analyze the imaging data. Preprocessing of each dataset included slice-timing offset correction, realignment estimation, normalization to the Montreal Neurological Institute (MNI) stereotactic space, and Gaussian smoothing to decrease variability between subjects and maximize overlap (full width half maximum = 8mm)

In the first level analysis, a temporal high pass filter (128s) was applied and head movement parameters were entered as regressors. Each condition was individually modeled by the canonical hemodynamic response function. One contrast was computed for every participant: auditory stimulation versus rest. Statistical threshold was set to $p<0.001$ (uncorrected).

A second-level random-effects analysis was computed including all participants. MNI coordinates for peak activations of the group analysis were extracted from the SPM statistics output and were transformed into Talairach coordinates.

Apart from this we performed an individual voxel-based analysis for every participant. For that aim we extracted the number of activated voxels per region from the SPM statistics output for the first-level analysis of every participant. The extracted numbers of activated voxels in each anatomical brain region were used for further statistical comparison of activation across the different lobes and the two hemispheres. The activation which was obtained only in the individual analysis, and not in the second-level group analysis, was inspected for individual differences (general activation of that region and location of activation in that region). Additionally, the activation obtained for different anatomical regions (e.g. inferior frontal gyrus) was investigated in detail to determine in which functional areas the activation was located (e.g. Broca's area).

This statistical analysis of individual voxel-based results was performed using SPSS (IBM SPSS Statistics 23). Paired t-Tests were used to compare the number of activated voxels for the two hemispheres.

8.3 Results

8.3.1 Group Analysis

A second-level random effects analysis of twenty participants ($p<0.001$ uncorrected) was computed in SPM (Figure 8.1). Activation occurred in the temporal, parietal, and frontal lobes. There was no BOLD signal change in occipital areas.

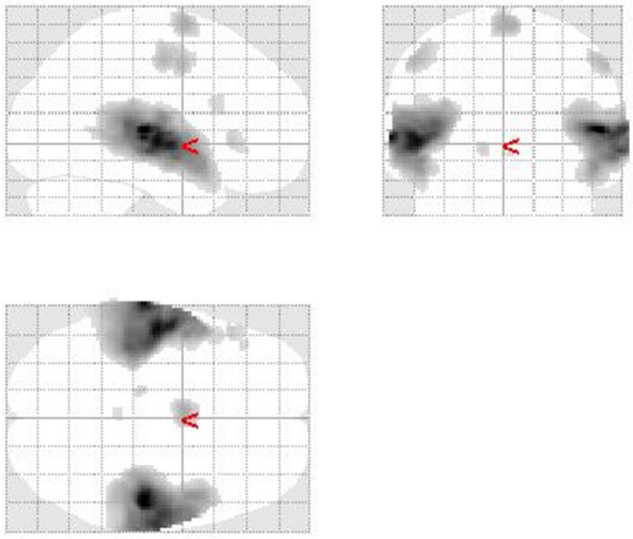

Figure 8.1: Group analysis for the contrast auditory > rest condition.

A detailed overview of peak activations is presented in Table 8.1. Middle and inferior frontal gyri as well as transverse temporal gyrus show activations only in the left hemisphere. The middle temporal gyrus shows activation only in the right hemisphere.

Table 8.1: Anatomical regions, Hemisphere, T-statistics (T) and Talairach coordinates (Tal) for contrast auditory > rest conditon

Anatomical Region	Hemisphere	T	Tal-x	Tal-y	Tal-z
Precentral Gyrus	L	5.4	-61	-3	11
Precentral Gyrus	L	6.2	-51	-9	47
Precentral Gyrus	R	6.2	53	0	42
Middle Frontal Gyrus	L	4.7	-46	1	50
Inferior Frontal Gyrus	L	5	-51	25	-1
Inferior Frontal Gyrus	L	3.9	-42	31	-7
Inferior Frontal Gyrus	L	4	-48	18	19
Inferior Frontal Gyrus	L	3.6	-53	11	20
between Superior and Medial Frontal Gyrus	R	7.1	2	3	64
Superior Temporal Gyrus	L	18.1	-51	-16	1
Superior Temporal Gyrus	L	17.1	-65	-23	3
Superior Temporal Gyrus	L	13.5	-44	-21	5
Superior Temporal Gyrus	L	9.4	-50	-1	-10
Superior Temporal Gyrus	L	9.3	-57	-30	14
Superior Temporal Gyrus	R	19.3	51	-23	9
Superior Temporal Gyrus	R	14.8	63	-15	6
Superior Temporal Gyrus	R	9	57	0	0
Superior Temporal Gyrus	R	8.6	50	3	-12
Middle Temporal Gyrus	R	14	63	-20	-4
Middle Temporal Gyrus	R	11.4	59	-6	-8
Transverse Temporal Gyrus	L	12.3	-42	-31	11
Midbrain	L	4.4	-14	-25	-4
between Culmen, Midbrain, Cerebellar Lingual, Midbrain, and Cerebellar Lingual	B	3.7	0	-39	-5

8.3.2 Voxel-based Analysis

In order to explore individual activation patterns in this group a single subject analysis was conducted for every participant and the number of activated voxels per region were extracted from the SPM statistics output.

An overview over the number of activated voxels across participants can be seen in Tables 8.2 (left hemispheric voxels) and 8.3 (right hemispheric voxels). Activation of the occipital lobe and subcortical structures was minor and therefore these were excluded from further analysis. Precentral and postcentral gyri, as well as superior, middle, and transverse temporal gyri and the left insula showed activated voxels in all twenty participants. Superior parietal lobule, paracentral lobule, and angular gyrus showed no activation. Highest values were obtained for the precentral and inferior frontal gyri in the frontal lobe. The highest values in the parietal lobe were obtained for the postcentral gyrus and inferior parietal lobule. In the temporal lobe the highest values were obtained from the superior temporal and transverse temporal gyri. The insula showed a very high activation as well (approximately same amount of activated voxels as in the precentral gyrus).

Table 8.2: Number of activated voxels for all participants and brain regions for the left hemisphere

Anatomical region	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	Mean
Precentral Gyrus	201	338	412	472	352	23	154	332	180	323	149	453	539	109	17	478	410	762	283	319	315 .3
Superior Frontal Gyrus	103	83	21	42	5	0	0	0	32	18	0	0	31	29	0	60	44	67	0	54	29 .45
Medial Frontal Gyrus	17	78	39	6	5	0	0	0	0	23	0	0	86	109	0	33	29	42	0	85	27 .6
Middle Frontal Gyrus	85	154	0	353	133	0	20	31	98	132	0	86	8	308	0	15	6	110	29	170	86 .9
Inferior Frontal Gyrus	639	270	59	296	108	0	0	333	204	577	8	569	456	76	0	229	384	788	73	144	260 .65
Postcentral Gyrus	77	272	169	235	88	75	307	231	311	39	196	233	420	74	179	84	106	639	279	214	211 .4
Inferior Parietal Lobule	260	237	253	247	21	117	322	109	75	21	115	153	141	0	13	0	0	671	31	154	147
Supramarginal Gyrus	11	34	31	286	7	15	0	0	0	4	0	66	5	0	22	0	0	273	0	0	37 .7
Precuneus	59	34	0	13	0	0	0	0	0	39	19	0	5	0	0	0	0	0	0	0	8 .45
Superior Temporal Gyrus	2184	2100	2899	2413	2056	1672	2290	2823	2489	2762	2077	2779	2624	1382	1719	1986	2060	2599	2078	2241	2261 .65
Middle Temporal Gyrus	959	891	1210	1340	1812	437	402	1307	1361	1631	896	1963	2393	839	147	1776	1877	1092	424	801	1177 .9
Inferior Temporal Gyrus	0	2	33	40	48	0	0	7	22	2	18	76	241	0	0	96	77	25	0	0	34 .35
Transverse Temporal Gyrus	212	222	197	213	185	158	210	203	214	168	193	200	212	146	161	197	209	237	208	223	198 .4
Insula	341	404	538	412	144	76	360	440	488	141	229	309	388	5	62	127	126	483	657	479	310 .45

Table 8.3: Number of activated voxels for all participants and brain regions for the right hemisphere

Anatomical region	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	Mean
Precentral Gyrus	309	285	242	288	67	3	239	329	214	215	137	293	351	314	131	370	321	528	247	189	253 .6
Superior Frontal Gyrus	36	57	88	19	0	0	16	0	0	3	0	0	41	35	0	12	9	43	0	67	21 .3
Medial Frontal Gyrus	0	1	56	16	0	0	0	0	0	12	0	0	41	49	0	32	0	28	0	36	13 .55
Middle Frontal Gyrus	123	216	42	157	88	0	61	30	177	253	0	219	19	86	1	6	3	170	8	200	92 .95
Inferior Frontal Gyrus	145	303	69	0	4	0	46	213	299	271	0	249	651	37	0	125	430	248	193	451	186 .7
Postcentral Gyrus	263	200	146	321	31	24	237	125	178	228	182	369	134	104	68	95	72	531	161	86	177 .75
Inferior Parietal Lobule	306	20	0	48	0	8	3	204	0	29	86	86	145	4	143	82	0	202	1	18	69 .25
Supramarginal Gyrus	31	0	0	0	0	0	0	2	0	0	0	0	49	0	12	0	0	6	0	0	5
Precuneus	0	40	0	0	2	0	0	0	0	0	0	0	8	0	0	0	0	0	1	0	2 .55
Superior Temporal Gyrus	2123	2022	2782	1991	1665	980	2081	2845	2074	2333	1213	2549	2707	1277	1637	2355	2214	2720	2025	2119	2085 .6
Middle Temporal Gyrus	679	837	1390	838	1565	804	691	1431	1023	1560	683	1334	2387	1085	40	1525	1497	902	616	950	1091 .85
Inferior Temporal Gyrus	0	54	111	0	35	0	11	40	0	47	7	1	143	0	0	26	17	1	0	0	24 .65
Transverse Temporal Gyrus	190	161	159	193	104	78	196	208	211	175	131	203	205	109	198	207	185	211	186	205	175 .75
Insula	591	347	346	146	133	4	415	424	450	206	30	549	331	0	172	88	182	478	384	308	279 .2

Comparison between Hemispheres

The number of activated voxels across hemispheres was compared for every brain region with a two-tailed paired t-test (Tables 8.2 and 8.3). Five brain regions showed significant differences between the two hemispheres (Figure 8.2). For all of them the left hemisphere presented a higher number of activated voxels than the right hemisphere. The precentral gyrus ($p=0.044$), medial frontal gyrus ($p=0.021$), inferior parietal lobule ($p=0.032$), superior temporal gyrus ($p=0.015$), and transverse temporal gyrus ($p=0.004$) were the brain regions with significant differences in activated voxels across both hemispheres. Inspection of the individual lateralization revealed that not all participants presented a left lateralization, but some displayed a right lateralization in: precentral gyrus (5), medial frontal gyrus (2), inferior parietal lobule (7), superior temporal gyrus (5) and transverse temporal gyrus (5). As only half of the participants showed activation in the medial frontal gyrus, the lateralization is not as strong as in the other regions (also apparent in figure 2). Although seven participants showed a lateralization to the right inferior parietal lobule, differences however were small in that direction (mean value for right lateralization of about 50 voxels) whereas lateralization to the left for the remaining participants was strong (mean value of left lateralization of about 160 voxels).

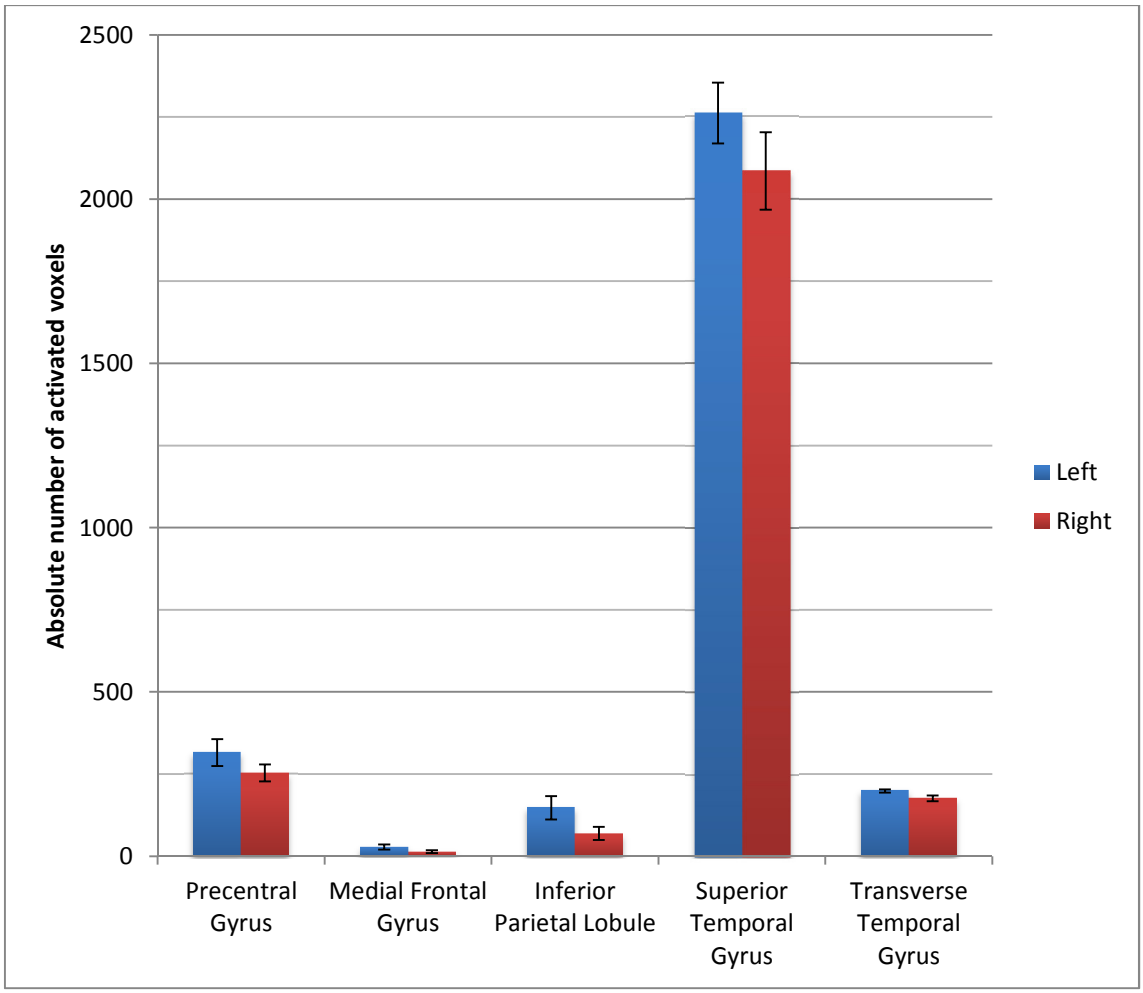

Figure 8.2: Significant differences in the number of activated voxels across both hemispheres for the contrast auditory > rest ($p<0.05$). Mean values activated voxels ± standard error of the mean are presented for both hemispheres separately.

Comparison of the different lobes

The number of activated voxels was calculated for every lobe in order to compare the different lobes with each other (only frontal, parietal, and temporal considered). An overview of the individual voxel-based results for each lobe can be seen in Figure 8.3. The frontal lobe included precentral gyrus, superior, medial, middle, and inferior frontal gyrus. Activation pattern in the parietal lobe consisted of voxels in the postcentral gyrus, inferior parietal lobule, supramarginal gyrus, and precuneus. Temporal lobe values were summed up over superior, middle, inferior, and transverse temporal gyri, and the insula. The number of activated voxels in the frontal lobe was 1288, while it was 659 in the parietal lobe and 7640 for the temporal lobe.

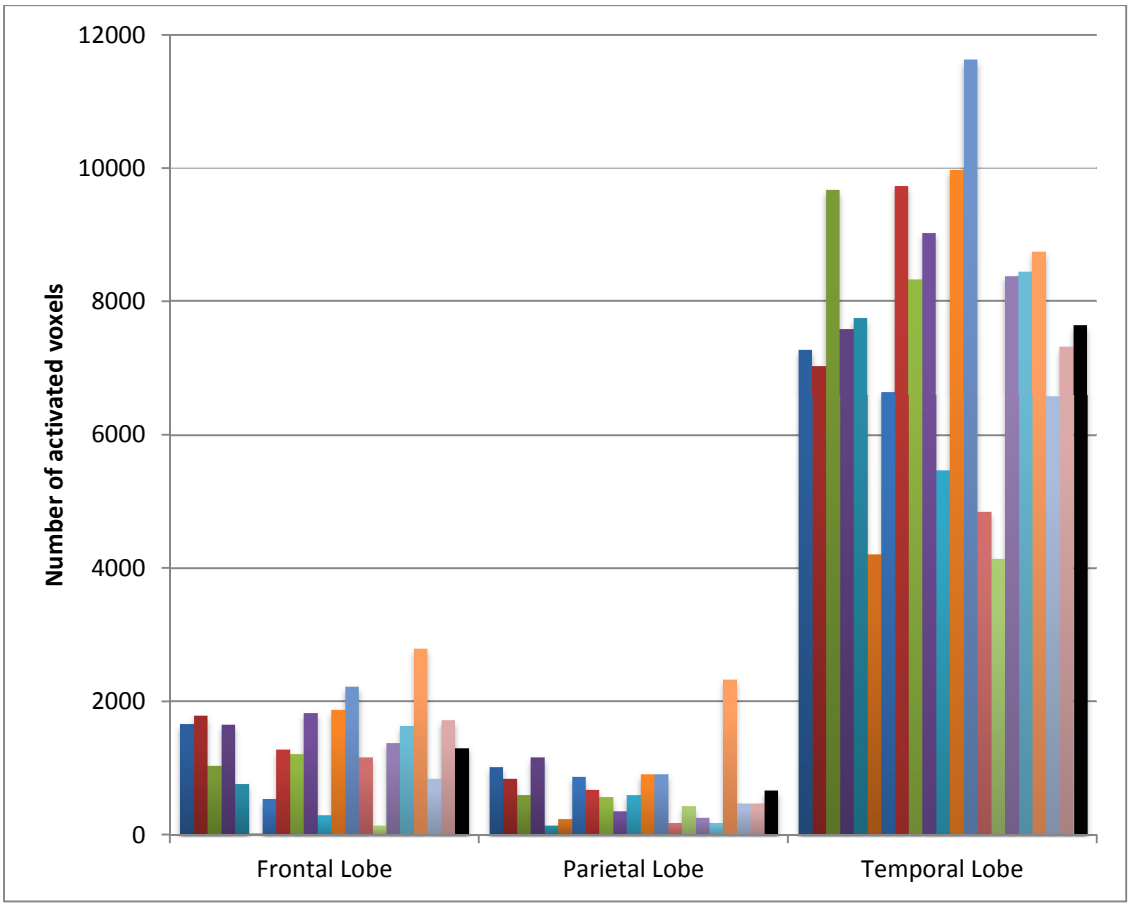

Figure 8.3: Number of activated voxels in frontal, parietal and temporal lobes for each participant. The black bars present the mean values for each lobe across all participants.

8.4 Discussion

This study was carried out in order to investigate the BOLD signal in healthy elderly participants in response to musical stimulation and to compare it with findings from the literature about the music perception network in young people. Additionally, individual voxel-based results served to explore the contribution of the different hemispheres and lobes to the processing of the musical input.

8.4.1 General Discussion

Generally, the activation pattern we obtained was distributed throughout temporal, frontal, and parietal areas, in line with previous research (Fedorenko, McDermott, Norman-Haignere, & Kanwisher, 2012; Foster & Zatorre, 2009; Koelsch, 2011; Lee et al., 2011; Platel et al., 1997; Schwenzer & Mathiak, 2011).

Activation in superior, middle, and transverse temporal gyri, the medial frontal gyrus, insula, pre- and postcentral gyri, and inferior parietal lobule may be attributed to the auditory and musical aspects of the presented material (LaCroix, Diaz, & Rogalsky, 2015). Other frontal areas may have been involved in attention, working memory, and other

executive functions which the participants may have engaged in during the passive listening task (and which we cannot exclude) (Janata, Tillmann, & Bharucha, 2002; LaCroix, Diaz, & Rogalsky, 2015; Platel et al., 1997).

Temporal activation

The processing of general auditory information and also musical input like pitch or timbre is accomplished by primary and secondary auditory cortices (Koelsch, 2011; Stewart et al., 2006; Stewart et al., 2008). The primary and secondary auditory cortices are located in the medial part of the Heschl's gyrus, which can be found in the superior temporal cortex. Areas right anterior and posterior to Heschl's gyrus in the superior temporal gyrus are also involved in melodic processing (Farbood, Heeger, Marcus, Hasson & Lerner, 2015). The planum temporale – which lies posterior to Heschl's gyrus – is responsible for melody and rhythm formation and grouping while the cognitive analysis of melodies is achieved by frontal areas (Koelsch, 2011; Clark, Golden, & Warren, 2015). Thus, the perception of single pitches and the grouping of tones to a melody are accomplished by temporal areas.

Insula activation was visible in all participants but one. The insula is involved in auditory processing as well, especially in terms of musical input and emotional music perception, but also in detecting irregular chords (Bamiou, Musiek, & Luxon, 2003; LaCroix, Diaz, & Rogalsky, 2015; Koelsch et al., 2005).

Frontal activation

Activation in the inferior frontal gyrus may be attributed to the verbal part of the musical stimulus, as we used a German song. Parts of Brodmann area 47 were activated in the group analysis, with some overlap with Broca's area for individual activations. Brodmann area 47 seems to be engaged in analyzing syntax and temporal order of music, as a melody evolves over time (Farbood, Heeger, Marcus, Hasson, & Lerner, 2015; Levitin & Menon, 2003; Vuust, Roepstorff, Wallentin, Mouridsen, & Østergaard, 2006). Parts of both Broca's and Wernicke's areas and their right homologues were activated, this might not only be due to speech comprehension of the German Musical, but also because they may have been involved in processing some basic musical features as well, e.g. syntax of the melody (Abrams et al., 2011; Maess, Koelsch, Gunter, & Friederici, 2001).

Parietal activation

Parts of the precentral gyrus, primary and supplementary motor areas were also activated. It is important to note that parietal activation became only visible in the individual voxel-based analysis and not at the group level. Although most of the

participants showed activated voxels, these voxels may not have overlapped sufficiently to become significant in the group analysis. Thus, in the individual voxel-based analysis we saw additional activation in the postcentral gyrus, the inferior parietal lobule, and the supramarginal gyrus. The primary and supplementary motor areas and supramarginal gyrus are involved in rhythm and beat perception (Bengtsson et al., 20009; Fedorenko et al., 2012; Grahn & Brett, 2009; Koelsch, 2011; Thaut, Trimarchi, & Parsons, 2014; Toiviainen, Alluri, Brattico, Wallentin, & Vuust, 2014; Zatorre, Chen, & Penhune, 2007). Possibly some participants paid attention to the beat, or subconsciously processed the underlying beat and rhythm of the song, while others did not. Otherwise some of them may have covertly tapped with their finger/hand/foot according to the beat, which may have not been the same finger/body part for every participant and hence no sufficient overlap appeared in the group analysis.

The inferior parietal lobule is concerned with contour perception (Diaz, & Rogalsky, 2015; Thaut, Trimarchi, & Parsons, 2014). Participants may have perceived the overall contour of the different melodic parts that were presented for short sequences of 20 seconds, enough time to follow the rhythm, melody and contour of that song.

Minor precuneus activation was seen in some participants, possibly because they visualized the musical scene which they were familiar with from the visual and bimodal conditions (which were not analyzed in this context), or used executive functions, or working memory. However, the precuneus is also involved in music processing (e.g. pitch and contour) which is highly connected to the other functions (Cavanna & Trimble, 2006; Platel et al., 1997).

Additionally, pre- and postcentral gyri showed activated voxels in every participant, while all other areas in frontal and parietal regions did not. Thus, pre- and postcentral gyri seem to be important in processing the musical input in our study, as they showed robust activation for all individuals. Young participants showed activation in these areas during passive music listening as well (LaCroix, Diaz, & Rogalsky, 2015).

8.4.2 Lateralization and Contribution of the Lobes

The second-level group analysis showed a left lateralization for middle and inferior frontal gyri, and the transverse temporal gyrus, while a right lateralization was seen for the middle temporal gyrus (table 1, Figure 1). A closer look at the individual voxel-based analysis partly reflected the results: significantly more activated voxels were found in five regions of the left hemisphere compared to the right hemisphere: Precentral and medial frontal gyri, inferior parietal lobule, superior, and transverse temporal gyri (Figure 2).

Temporal lobe activation was highest in our paradigm. Superior, middle, and transverse temporal gyri showed robust activation in every participant. Thus, most of the processing work is done in the temporal lobe due to basic encoding of music properties like pitch but also melodic and rhythmic grouping (Koelsch, 2011). Frontal areas play a major role, although no active task was required in our experiment. Activation was seen in almost all individuals and a high amount of voxels in the frontal lobe was activated. This may partly result from the fact that frontal areas are the preferred projection fields of temporal areas (Platel et al., 1997) and many frontal areas are involved in processing musical input. Thus, higher cognitive analysis of the musical input (concerning music, language, attention or working memory) took definitely place. Interestingly, also some parietal areas make a major contribution to the processing of the musical input, although other parietal areas were not activated at all (these were superior parietal lobule, paracentral lobule, and angular gyrus). The highest number of activated voxels was obtained for the precentral and inferior frontal gyri in the frontal lobe; for the postcentral gyrus and inferior parietal lobule in the parietal lobe; and for the superior temporal and transverse temporal gyri in the temporal lobe. Most of these areas showed lateralization effects in the second-level analysis or in the individual voxel-based analysis. Thus, highest contributions to the processing of the musical input arise from left lateralized brain regions in frontal, parietal, and most importantly temporal areas.

Lateralization issues have always been under debate, because some studies find lateralization effects of specific functions for music processing, while others do not (Alossa & Castelli, 2008; García-Casares et al., 2013; Johnsrude, Penhune, & Zatorre, 2000; Stewart et al., 2006). Mostly the right hemisphere was thought to be involved in music perception, suggested to be a counterpart for left lateralized speech perception (LaCroix, Diaz, & Rogalsky, 2015), although substantial overlaps between music and speech perception were identified as well (Fadiga, Craighero, & D'Ausilio, 2009; Fedorenko, Patel, Casasanto, Winawer, & Gibson, 2009; Koelsch, 2011; Peretz, Vuvan, Lagrois, & Armony, 2015). Left lateralization of prefrontal and inferior frontal areas in our study may partly be due to the verbal material we used and the fact that all participants were right-handed (thus possible covert tapping to the beat may have occurred for right body parts). But we do not only find this lateralization for areas engaged in speech perception. Although we cannot disentangle speech from music perception in this paradigm, the left lateralization for many regions in temporal, parietal, and frontal areas speaks for a specific music-related lateralization correlated beyond the processing of the verbal material.

8.4.3 Differences between elderly and young people

Sikka and colleagues found higher activation in the left superior temporal gyrus for young participants and higher activation in left superior frontal, left angular, and bilateral superior parietal regions for older adults (Sikka, Cuddy, Johnsrude, & Vanstone, 2015). We did not find angular and superior parietal activation at all and only minor superior frontal activation. This may partly result from the different task we applied (passive listening versus melody recognition). Our task was supposed to activate the inferior frontal gyrus bilaterally, left medial frontal gyrus, right middle frontal gyrus, bilateral insula, right pre- and bilateral postcentral gyri, and left inferior parietal lobule (LaCroix, Diaz & Rogalsky, 2015). Our results show a shift to the left hemisphere for prefrontal, inferior, and middle frontal gyri. All other regions are in accordance with right/left/bilateral activation in the literature. Thus, we definitely see a higher engagement in left frontal areas (Grady, 2008). However, we saw an increased lateralization in our task and participants although we expected a decreased lateralization in older adults.

Whether or not the high engagement of frontal areas differs significantly from that of healthy young participants cannot be resolved at this stage. Additionally, the question whether or not differences between young and old adults arise because of differences in experience and in evoked associations (which is definitely higher in the older population) or due to other functional mechanisms cannot be solved yet. The absence of decreased lateralization can be explained by our easy task. Due to the choice of the passive listening task no compensational mechanisms may have been needed, but it could also be the case that for the pure perception of music elderly people do not need to make use of compensatory mechanisms at all. Additionally, other reorganization principles may underlie the perception of music in elderly people not comparable to other cognitive functions we have been explored so far. Future studies may resolve this issue by applying varying task demands for young and elderly people and evaluate behavior as well as the BOLD signal during the different tasks.

8.4.4 Conclusion

We conclude that the applied method (especially individual voxel-based analysis) is a very appropriate way to detect contributions of different brain areas in each hemisphere to a specific task. This is particularly interesting because individual differences in the representation of music perception exist (Schuppert et al., 2000; Toivianinen, Alluri, Brattico, Wallentin, & Vuust, 2014) and because music perception is accomplished by a widely distributed network which needs to be further specified. Our results show that highest contributions to the processing of musical input during passive listening result from left lateralized activation in frontal, parietal, and temporal brain regions. Temporal

activation was highest, followed by frontal and parietal activation. Pre- and postcentral regions seem to play a major role in this task. Furthermore, an increased lateralization and high engagement of frontal areas is seen in elderly participants compared to the activation in young people presented in the literature. These results can be seen as an encouragement for further research into the fascinating and highly complex topic of music perception.

Discussion and Conclusion

"Music does not just express static emotions or affects such as nobility or gloom. It moves from one state to another in kaleidoscopic patterns of tension and attraction that words cannot begin to describe adequately."

Ray Jackendoff & Fred Lerdahl

9. Discussion

The objective of the current dissertation was twofold: investigations of 'amusia' and its effects on other functions and areas of the brain with behavioral testing and fMRI. The first manuscript entitled "Musical, visual and cognitive deficits after middle cerebral artery infarction" dealt with the behavioral assessment and investigated the relationship of amusia, visual, and cognitive deficits. The second manuscript "Amusia after stroke – an fMRI study" included fMRI measurements and explored changes in brain activation resulting from stroke and amusia. The third manuscript "Lateralization of music perception in healthy elderly people – an fMRI study" explored the fMRI activation pattern in healthy elderly participants.

Results of these experiments are presented and discussed in the following sections. However, a theoretical update about music perception literature is given first. The last chapter provides an integration of literature and results obtained within this dissertation, in addition to suggestions for future research.

9.1 General Discussion

Having a closer look at the literature and areas that are found to be involved in music perception, one recognizes that almost all temporal, frontal, and parietal regions besides some subcortical structures are involved. Much of this work was published within the last three years (when the dissertation project had already started), especially involving the suggestions for the music processing model (Clark, Golden, & Warren, 2015; García-Casares et al., 2013). It is not the scope of the present thesis to elaborate on all brain regions found to be involved in music processing in the specific literature because the focus of this dissertation is on amusia and related implications. However, the main findings have been clearly summarized and are presented in the following:

- **Inferior frontal gyrus**: Pitch and harmony perception (Koelsch et al., 2005; LaCroix, Diaz, & Rogalsky, 2015; Peretz, Vuvan, Lagrois, & Armony, 2015; Platel, 1997); Rhythm perception (Thaut et al., 2014); Both auditory and visual object semantic material (Adams & Janata, 2002)
- **Medial frontal gyrus**: Passive listening to music (LaCroix, Diaz, & Rogalsky, 2015); Rhythm perception (Thaut et al., 2014); Musical memory (Platel, Baron, Desgranges, Bernard, & Eustache, 2003)
- **Middle frontal gyrus**: Rhythm perception (Thaut et al., 2014)

- **Superior frontal gyrus**: Musical memory (Platel, Baron, Desgranges, Bernard, & Eustache, 2003)
- **Precental gyrus**: Musical structure (Fedorenko et al., 2012; Koelsch et al., 2005); Rhythm perception (Bengtsson et al., 2009; Grahn & Brett, 2009; Thaut et al., 2014; Zatorre, Chen, & Penhune, 2007); Passive listening to music (LaCroix, Diaz, & Rogalsky, 2015)
- **Postcentral gyrus**: Musical structure (Fedorenko et al., 2012); Rhythm perception (Bengtsson et al., 2009; Thaut et al., 2014; Grahn & Brett, 2009; Zatorre, Chen, & Penhune, 2007); Passive listening to music (LaCroix, Diaz & Rogalsky, 2015)
- **Precuneus**: Pitch and harmony detection (Cavanna & Trimble, 2006; Platel, 1997; Thaut et al., 2014); Musical memory (Platel et al., 2003)
- **Insula**: Auditory processing, especially with musical input; musical meaning and emotional music perception (Bamiou, Musiek, & Luxon, 2003; LaCroix, Diaz, & Rogalsky, 2015; Koelsch et al., 2005; Thaut et al., 2014)
- **Supramarginal gyrus**: Musical meaning and emotional music perception (Koelsch et al., 2005); Rhythm perception (Thaut et al., 2014)
- **Angular gyrus**: Musical memory (Platel et al., 2003)
- **Inferior parietal lobule**: Contour perception (LaCroix, Diaz, & Rogalsky, 2015; Lee et al., 2011; Thaut et al., 2014)
- **Superior parietal lobule**: Auditory spatial and attentional functions, pitch perception (Gaab et al., 2003)
- **Intraparietal sulcus**: Pitch perception (Foster & Zatorre, 2009; Schwenzer & Mathiak, 2011)
- **Superior temporal areas**: Musical meaning and emotional music perception, contour and rhythm perception (Fedorenko et al., 2012; Koelsch et al., 2005; Koelsch et al., 2011; Lee et al., 2011; Platel, 1997; Schwenzer & Mathiak, 2011; Stewart et al., 2008; Thaut et al., 2014; Toiviainen, Alluri, Brattico, Wallentin, & Vuust, 2014)
- **Middle temporal gyrus**: Musical structure (Fedorenko et al., 2012); Rhythm perception (Thaut et al., 2014); Musical memory (Platel et al., 2003)
- **Transverse temporal gyrus**: Rhythm perception (Thaut et al., 2014)
- **Basal ganglia**: Rhythm perception (Grahn & Brett, 2009; Zatorre et al., 2007)
- **Cerebellum**: Rhythm perception (Bengtsson et al., 2009; Grahn & Brett, 2009; Thaut et al., 2014; Toiviainen, Alluri, Brattico, Wallentin, & Vuust, 2014; Zatorre, Chen, & Penhune, 2007)

In addition to the above listed publications it is worth to point out that human sounds and speech recruit a network of posterior superior temporal sulci, fronto-parietal regions, insula, and sub-cortical regions (Belin, Zatorre, Lafaille, Ahad, & Pike, 2000; Desai, Liebenthal, Waldron, & Binder, 2008; Engel, Frum, Puce, Walker, & Lewis, 2009; Lewis, Brefczynski, Phinney, Janik, & DeYoe, 2005; Lim, Fiez, & Holt, 2014). This temporal-frontal-parietal network is usually involved in domain-general attention and working memory outside of music processing (Janata, Tillmann & Bharucha, 2002). This knowledge is further complicated by individual differences in the representation of music perception (Schuppert et al., 2000; Toivianinen, Alluri, Brattico, Wallentin, & Vuust, 2014).

9.2 Behavioral Measurements

The key elements of the behavioral measurements were two subtests (scale and rhythm) from the MBEA. Additionally, a large battery of other cognitive and perceptual tests was conducted to find out whether amusia deficits are a) selective for musical input, b) better described by a general perceptual dysfunction, c) due to WM deficits, or d) the result of deficits in attention. For this aim a visual Gestalt perception test, a categorization task with four different modalities (auditory, visual, verbal, and nonverbal) and tests for WM and attention were applied to patients suffering from a stroke in the supply area of the middle cerebral artery.

Full data were acquired for twenty stroke patients suffering small cerebral artery infarctions. In these investigations we found two amusic patients who did not present any other deficits. Other stroke patients with attention or WM deficits were not impaired in the MBEA. Additionally, lesion analysis showed small areas within the basal ganglia, namely putamen and globus pallidus, which seem to be involved in rhythm perception. We conclude that we found cases of ‘pure amusias’ with selective impairment in music perception induced by small lesions in the frontal lobe or basal ganglia. Minor deficits in WM or attention do not necessarily lead to low performances in the MBEA. Thus, relatively pronounced lesions are able to damage a specific music area responsible for a specific sub-function within the music perception network. This area can be embedded in a brain region involved in other cognitive functions as well, i.e. large lesions of this region can lead to several different deficits, and it can be particularly small. Some regions in the brain are relatively large and complex, thus they can easily engage in more than one function or distinct processing network (Peretz, Vuvan, Lagrois & Armony, 2015). Therefore any particular form of ‘pure amusia’ is relatively rare (as can be seen by only two amusic patients found within a pool of twenty-five measured stroke patients) but cases of amusia

presenting a multifaceted picture of deficits (as presented in the literature) actually denote a form of 'non-pure amusia'.

In contrast to the literature, we were not able to identify many amusia patients (in the literature up to 60 % of the investigated stroke patients were classified as amusia patients) nor did we find correlated deficits in visual or cognitive functions in our stroke patients with amusia. Twenty-five patients were screened with the MBEA and only two presented deficits classified as being amusic. Thus, our original aim of differentiating between deficits in the MBEA according to a) musical deficits, b) attention deficits, c) WM deficits, and d) general perceptual deficits could not be addressed within this dissertation.

A major reason for finding only two amusia patients could be the assessment of patients with small lesions. Previous studies investigated stroke patients with larger lesions than we did and it could be the case that these lesions damaged a large array of functions which are anatomically close but functionally distinct. This could explain why 1) many amusic patients and 2) amusic patients with other deficits in attention, memory, language, and visual perception were found in these studies (Särkämö et al., 2009a; Särkämö et al., 2009b; Särkämö et al., 2010). Assessment of small lesions is advantageous and disadvantageous at the same time. The likelihood of finding damage in a brain area involved in music perception rises with exploring large lesions, but the likelihood of discovering other compromised functions increases as well Thus, the likelihood of finding amusia patients decreases with the assessment of small lesions, but enables a more precise localization of the neuronal correlate of the disorder.

Another important aspect to keep in mind is to exclude that basic auditory deficits could also lead to low performance in the MBEA without being amusic per se. Särkämö et al. (2009a) found a significantly higher incidence of auditory cortex lesions in the amusia group but did not perform a test for basic auditory function (e.g. audiometry). Thus, it could not be excluded in their study that patients with general deficits in hearing acuity were falsely classified as being amusic. In order to rule out basic auditory deficits as a cause for low performance in the MBEA we applied audiometry in all our clinical investigations.

A last reason why we did not find many amusia patients could be simply the fact that the investigated stroke patients did not have their lesions in the regions where musical input is being processed or that these lesions were too small to induce major deficits. Inclusion criteria for participating in investigations for this dissertation did not only address lesion

location but also the general ability of the patient to participate in the applied tests (besides the willingness of the patient to participate of course). Thus, the well-being of the patient was always considered and let to exclusion of some of them due to increased stress. Within the scope of this dissertation no further investigations were possible.

9.3 Functional Magnetic Resonance Imaging

After release from the hospital, the stroke patients were invited to participate in an fMRI experiment at the University of Bremen to assess the BOLD signal of different brain regions in response to visual and auditory stimulation. The aim was to investigate in which brain areas amusic patients show an abnormal (increased or decreased) BOLD signal compared to other stroke patients and healthy controls.

The comparison of amusic stroke patients, non-amusic stroke patients, and healthy controls yielded an interesting pattern of activation obtained from unimodal and bimodal visual and auditory stimulation. Pre- and postcentral gyri seem to be important in processing the musical input of our stimuli (German musical). Activation in temporal, occipital, fusiform, and postcentral gyri in response to unimodal stimulation was increased for stroke patients compared to healthy controls. On the other hand, bimodal stimulation led to decreased temporal, precentral, angular, occipital, and precuneus activation in stroke patients compared to healthy participants.

Due to lesion sites and different BOLD signal characteristics for unimodal and bimodal stimulation, we conclude that higher levels of activation are a sign of compensation needed for the successful processing of unimodal information. Decreased activation can be found in damaged and nearby regions for bimodal activation during which information of the unaffected modality suffices for processing of the stimuli.

One amusic stroke patient with rhythm perception deficit showed increased activation in frontal and parietal areas (including pre- and postcentral gyri) in response to unimodal auditory stimulation, which was significantly different from all other patients and participants. This activation dropped after six months, but activation in the inferior parietal lobule (IPL), supramarginal gyrus and insula were still higher than for the other participants. Musical abilities of this patient recovered after six months and changes in brain activation were found for both hemispheres. From the literature we know that rhythm perception is closely related to activation in supramarginal gyrus, premotor and supplementary motor areas, as well as precuneus, and IPL (Fedorenko et al., 2012; Grahn & Brett, 2009; Thaut et al., 2014; Zatorre, Chen, & Penhune, 2007). Within these areas distinct neural substrates process sub-elements of rhythm (like meter or beat) (Bengtsson

et al., 2009; Thaut et al., 2014). Additionally, there are anatomical connections between basal ganglia and IPL, frontal areas, and premotor and supplementary motor areas (Karnath et al., 2005; Ward et al., 2003).

Thus, the initial recruitment of frontal and parietal areas could be a compensatory mechanism in response to musical input, also seen in other stroke patients compared to healthy controls for unimodal but not for bimodal stimulation. From the results of the re-test after six months one may conclude that additional 'rhythm perception areas' are recruited efficiently now because no musical deficit can be observed. Our results highlight the connection of basal ganglia to supramarginal gyrus and IPL. These areas seem to work closely together, possibly undergoing similar tasks within the function of rhythm perception. Damage to any of these areas can cause deficits in the perception of rhythms, but the other areas may be able to take over the lost function and to re-establish the successful processing of rhythms. High insula activation was also seen in another amusic patient displaying melodic and rhythmic problems. Therefore, we conclude that the insula may play an important role in amusia in general – possibly due to the strange and unpleasant perception of music.

As already mentioned in the introduction of this dissertation, the BOLD signal in stroke patients needs to be interpreted with caution. Several studies have shown that neurovascular coupling – the relationship between blood flow and oxygen concentration – can be changed in aging or disease and changes in the acquired BOLD signal were observed (Carusone et al., 2002; D'Esposito, Deouell, & Gazzaley, 2003; Fabiani et al., 2014; Hamzei et al., 2003; Handwerker et al., 2012; Murata et al., 2006). Additionally, the stroke and the accompanied arterial deposits may alter the BOLD signal. But with careful inspection of the data, the BOLD signal can be an effective tool to investigate the brain function of stroke patients compared to healthy controls. The obtained results in this dissertation cannot be explained by a general abnormal neurovascular coupling due to several reasons. First, the increased signal was only obtained for one specific condition and not for all kinds of stimulations. Second, the signal was only increased in frontal and parietal regions, but not in temporal and occipital regions. Finally, recovery of the signal (approaching to a value of the healthy participants) was only present in a few regions but not in all regions which showed increased signal in the sub-acute stage. Based on the exploration of the results, these (careful) conclusions have been made.

The investigation of voxel based results for twenty elderly healthy participants showed that highest contribution to the processing of the musical input in our study came from left lateralized activations in the frontal (precentral and inferior frontal gyri), parietal (postcentral gyrus and inferior parietal lobule), and temporal lobe (superior temporal and transverse temporal gyri). Temporal activation was highest, followed by frontal and parietal activation. Again, pre- and postcentral regions seem to play a major role in this task as all participants showed activations in these areas. Additionally, an increased lateralization and high engagement of frontal areas was seen in elderly participants compared to activation in young volunteers presented in the literature.

10. Conclusion

The integration of the results obtained with behavioral and fMRI measurements enables to consider the deficit of acquired amusia in a broader context. In short, we find that deficits found in amusia can be selective and are not generally related to deficits in attention, WM or visual perception. Additionally, stroke in frontal areas and basal ganglia may induce amusia symptoms and changes in brain activation that accompany amusia are found in frontal and parietal lobes. Specifically, the IPL, the supramarginal gyrus, and the insula are important brain areas still showing differences in brain activation after the amusia recovered six months after the initial stroke.

Considering these findings in context, current knowledge of the network for music perception can be extended. The models proposed for music perception involved temporal and frontal areas, as well as cerebellum, and basal ganglia (Clark, Golden, & Warren, 2015; García-Casares et al., 2013; Koelsch, 2011; Stewart et al., 2006). Other studies already pointed out that also premotor, supplementary motor (Fedorenko et al., 2012; Grahn & Brett, 2009; Zatorre, Chen, & Penhune, 2007) and parietal areas (Foster & Zatorre, 2009; Lee et al., 2011; Schwenzer & Mathiak, 2011; Thaut, Trimarchi, & Parsons, 2014) actively engage in specific sub-functions of musical perception. Furthermore, it was shown that attentive listening to music is achieved by a network of frontal, temporal, and parietal areas, which are usually involved in domain general cognitive functions like attention and WM (Janata, Tillmann, & Bharucha, 2002).

Results from behavioral data and lesion analysis indicate that certain brain areas execute specific sub-functions of music perception and that some of these areas are relatively small (e.g. small areas in putamen and globus pallidus). Focal lesions may specifically damage the area important for a specific sub-function of music perception, but larger

lesions more likely damage several distinct but anatomically close brain areas which are not responsible for similar or related functions. Based on fMRI results this dissertation highlights a network of supramarginal gyrus, IPL, and basal ganglia which is responsible for sub-functions of rhythm perception. Furthermore, the parietal lobe is involved in compensatory and reorganization mechanisms.

Hence, our results support the *modular* view of the music perception network recruiting a large array of non-lateralized brain areas in temporal, frontal and parietal areas (Clark, Golden & Warren, 2015; Peretz & Coltheart, 2003; Piccirilli, Sciarma, & Luzzi, 2000). Sub-functions are accomplished by several modules working together but damage to only one of these sub-modules can lead to amusic symptoms. Additionally, we saw that if a stroke damaged a specific area and the function was not sufficiently executed for a certain time, the unaffected modules are able to reorganize and to re-establish the concerned sub-functions (compensatory mechanism). With increasing age, the lateralization of functions within temporal, parietal and frontal regions may occur (further investigation is needed).

I cannot exclude that the two amusia patients actually presented deficits in some task which I did not access, i.e. these two cases might not have been 'pure amusia patients' either. This would imply that brain areas defined as being a module for a specific music perception sub-function are actually no pure music modules but also subserve other functions. It is certainly possible that at least some brain areas use the same neuronal resources to conduct different functions. But from the combination of results from behavior, lesion analysis, and fMRI, I conclude that our brain comprises small, distinct, and connected modules for specific sub-functions of music perception. Not only greater sub-modules processing melody, rhythm, timbre, harmony, etc., but still smaller sub-modules for the perception of rhythm exist (that would actually make them sub-sub-modules). Hence, it seems to be unlikely – although not impossible – that there are small areas in the brain processing a (sub-) sub-function of music and also another cognitive function (one that I did not access within my investigations).

In summary, a huge network including temporal, frontal and parietal regions is involved in processing musical input. Some of them are also engaged in other cognitive functions, e.g. attention and working memory or other music related abilities like singing or rehearsing. Certain functions have been differentiated across the brain (e.g. dissociation between rhythm and melody perception), but a few areas seem to be involved in more than one musical function. Therefore a disentanglement of executive functions, attention, working memory and language perception from active processing of musical input and a

differentiation of different musical functions in separated brain areas seem to be the next steps in research about music perception. Individual differences in musicality and possibly affinity to music always need to be kept in mind.

As frontal regions seem to be highly involved in the cognitive aspects of music perception, not only investigations of stroke patients with frontal lobe lesions may be appropriate, but also other patient groups like patients suffering fronto-temporal dementia seem to be highly interesting (Agustus et al., 2015; Downey et al., 2013; Omar, Hailstone, Warren, Crutch, & Warren, 2010). A detailed analysis of intact and damaged brain regions in relation to intact and impaired performance in music perception seems to be one major research method to find out which areas in the music perception network are needed to establish a sufficient perception of music and which areas lead to impaired performances when damaged. Additionally, individual and voxel based analyses are helpful to investigate the differences across participants and the different contributions of the different lobes and hemispheres (like in manuscript 3). Furthermore the processing of subcomponents of music can be investigated by confronting subjects with different types of music which lean more or less heavily on rhythm, melody and pitch variations during fMRI. Another idea would be to use the same set of musical stimuli but a change in attention focus (e.g. in the first run the participants are asked to attend to the underlying beat and in the second run they should focus their attention on the rhythmic structure).

As said in the introduction ‘any model can only be preliminary and any new patient with specific deficits will add knowledge to it’, further work with amusia patients is needed to extend the current model of music perception and amusia. A systematic investigation of lesion location, lesion size, and lateralization with respect to behavioral deficits and changes in brain activation present after a stroke will give new insights into the perception of music and its associated dysfunctions.

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Appendix

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B. Declaration of Authorship

Hiermit erkläre ich, dass ich die Doktorarbeit mit dem Titel:

„Dysfunctions of visual and auditory Gestalt perception (amusia) after stroke – Behavioral correlates and functional magnetic resonance imaging“

selbstständig verfasst und geschrieben habe und außer den angegebenen Quellen keine weiteren Hilfsmittel verwendet habe.

Ebenfalls erkläre ich hiermit, dass es sich bei den von mir abgegebenen Arbeiten um drei identische Exemplare handelt.

_____ _____

Ort, Datum Unterschrift