Neural mechanisms of age-related hearing loss and tinnitus: Insights from neuroimaging

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Summary

Age-related hearing loss is one of the most prevalent chronic disorders in the older population and is described as a form of bilateral sensorineural hearing loss affecting the higher frequencies (above 2 kHz). One of the causes for age-related hearing loss is damage to the cochlea or auditory nerve due to daily noise exposure over time. Tinnitus is the phantom perception of sound that is mostly perceived as hissing, buzzing or ringing "in the ear" without any external stimulation. Primary causes for tinnitus are hair cell damage followed by hearing impairment due to age-related changes – such as age-related hearing loss – or loud noise exposure. Hearing loss affects 40% of adults above the age of 65 years and is one of the major risk factors for chronic tinnitus which affects approximately 10-15% of the adult population. Hence, there is a close relationship between hearing loss and chronic tinnitus. However, not all hard of hearing individuals develop chronic tinnitus. In fact, about 90% of individuals with chronic tinnitus also experience hearing loss while only 30-40% of hard of hearing individuals suffer from chronic tinnitus. Thus, it is crucial to dissociate tinnitus from hearing loss in hearing research – especially when investigating their underlying neural mechanisms.

This habilitation thesis presents research on neural mechanisms of age-related hearing loss and chronic tinnitus investigated by functional magnetic resonance imaging. The different chapters of this thesis cover studies on neuroanatomical, task-based neural activity and resting state functional connectivity changes in age-related hearing loss along with findings from hearing aid fitting. Further, this thesis presents anatomical as well as resting state functional coupling alterations in relation to the tinnitus perception, tinnitus distress and cognitive abilities. The thesis thereby provides valuable insights into neural mechanisms of mild to moderate age-related hearing loss and chronic tinnitus. Important brain regions in hearing loss are the frontal cortex, auditory cortex and several resting state networks such as the dorsal attention network, while in chronic tinnitus the frontal cortex, the fornix, the precuneus and the default mode network seem to play significant roles.

To summarize, there seem to be more profound neural changes associated with chronic tinnitus than with age-related hearing loss and different brain regions seem to be important. Nevertheless, the findings also indicated similarities: such that the middle frontal gyrus might play an important role in both tinnitus and hearing loss although the underlying mechanism might be different. In addition, changes in resting state functional connectivity may not be associated with the hearing loss or chronic perception of tinnitus per se, but are related to the consequences of those – such as increased listening effort, changes in audiovisual integration and cognitive abilities. Hence, this habilitation thesis provided novel insights into neural mechanisms of hearing loss and tinnitus that are crucial for advancing treatment options as well as evaluating the efficacy of hearing loss and tinnitus interventions.

Zusammenfassung

Altersbedingter Hörverlust ist eine der häufigsten chronischen Erkrankungen in der älteren Bevölkerung und wird als eine Form von beidseitigem sensorineuralem Hörverlust beschrieben, der die höheren Frequenzen (über 2 kHz) betrifft. Eine der Ursachen für altersbedingten Hörverlust ist die Schädigung der Cochlea oder des Hörnervs durch die tägliche Lärmbelastung über die Lebensspanne. Tinnitus ist eine Phantomwahrnehmung von Geräuschen, die meist als Zischen, Summen oder Klingeln „im Ohr“ wahrgenommen wird, ohne dass eine externe Stimulation erfolgt. Die Hauptursache für Tinnitus ist eine Schädigung der Haarzellen, gefolgt von einer Beeinträchtigung des Gehörs aufgrund altersbedingter Veränderungen – wie altersbedingter Hörverlust – oder starker Lärmbelastung. Altersbedingter Hörverlust betrifft 40 % der Erwachsenen über 65 Jahren und ist einer der Hauptrisikofaktoren für chronischen Tinnitus, von dem etwa 10-15 % der erwachsenen Bevölkerung betroffen sind. Es besteht also ein enger Zusammenhang zwischen Hörverlust und chronischem Tinnitus. Allerdings entwickeln nicht alle schwerhörigen Menschen einen chronischen Tinnitus. Tatsächlich haben etwa 90 % der Personen mit chronischem Tinnitus auch einen Hörverlust, während nur 30-40 % der Schwerhörigen ebenfalls an chronischem Tinnitus leiden. Daher ist es von entscheidender Bedeutung, Tinnitus und Hörverlust in der Hörforschung voneinander zu trennen – insbesondere bei der Untersuchung der zugrundeliegenden neuronalen Mechanismen.

In dieser Habilitationsschrift werden Forschungsarbeiten zu neuronalen Mechanismen von altersbedingtem Hörverlust und chronischem Tinnitus vorgestellt, die mittels funktioneller Magnetresonanztomographie untersucht wurden. Die verschiedenen Kapitel dieser Arbeit umfassen Studien zu Veränderungen in neuroanatomischen Maßen, aufgabenbasierter neuronaler Aktivität und funktioneller Konnektivität während des Ruhezustands bei altersbedingtem Hörverlust sowie Erkenntnisse aus der Hörgeräteanpassung. Außerdem werden in dieser Arbeit Veränderungen in anatomischen Maßen und funktioneller Ruhezustands-Netzwerke in Bezug auf die Wahrnehmung des Tinnitus, die Belastung durch den Tinnitus und die kognitiven Fähigkeiten dargestellt. Diese Arbeit liefert damit wertvolle Einblicke in die neuronalen Mechanismen von leichtem bis mittelschwerem altersbedingten Hörverlust und chronischem Tinnitus. Wichtige Hirnregionen bei Hörverlust sind der frontale Kortex, der auditorische Kortex und verschiedene Ruhezustandsnetzwerke wie das dorsale Aufmerksamkeitsnetzwerk, während bei chronischem Tinnitus der frontale Kortex, der Fornix, der Precuneus und das Default-Mode-Netzwerk eine wichtige Rolle zu spielen scheinen.

Zusammenfassend lässt sich sagen, dass es bei chronischem Tinnitus offenbar ausgeprägtere neuronale Veränderungen gibt als bei altersbedingtem Hörverlust, und dass unterschiedliche Hirnregionen von Bedeutung sein könnten. Dennoch weisen die Ergebnisse auch auf Gemeinsamkeiten hin: So scheint der mittlere frontale Gyrus sowohl bei Tinnitus als auch bei Hörverlust eine wichtige

Rolle zu spielen, auch wenn der zugrundeliegende Mechanismus vermutlich unterschiedlich sind. Darüber hinaus könnten Veränderungen der funktionellen Konnektivität im Ruhezustand nicht mit dem Hörverlust oder der chronischen Tinnitus Wahrnehmung an sich in Verbindung stehen, sondern mit den Folgen davon - wie z. B. erhöhte Höranstrengung, Veränderungen der audiovisuellen Integration und der kognitiven Fähigkeiten. Diese Habilitationsarbeit lieferte somit neue Erkenntnisse über die neuronalen Mechanismen von Hörverlust und Tinnitus, die für die Weiterentwicklung von Behandlungsmöglichkeiten sowie für die Beurteilung der Wirksamkeit von Interventionen für Hörverlust und Tinnitus von entscheidender Bedeutung sind.

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1. Introduction

Age-related hearing loss is one of the most prevalent chronic disorders in the older population and affects 40% of adults above the age of 65 years (von Gablenz & Holube, 2015). It is commonly described as a form of bilateral sensorineural hearing loss that affects higher frequencies (above 2 kHz). The decrease in hearing abilities is idiopathic but may be caused by damage to the cochlea or the auditory nerve that arises from everyday noise exposure over time (Eckert et al., 2019).

Tinnitus is the phantom perception of sound that is mostly perceived as hissing, buzzing or ringing "in the ear" when there is no external stimulation. Chronic tinnitus affects approximately 10-15 % of the adult population and up to 45 % in the elderly population (Chang et al., 2019; Jafari et al., 2019; Knipper et al., 2020). One of the peripheral causes for tinnitus is hair cell damage followed by hearing impairment due to age-related changes – as for instance age-related hearing loss – or loud noise exposure (Knipper et al., 2020).

Thus, hearing loss and chronic tinnitus seem to be closely related to each other. In fact, hearing loss is a commonly identified risk factor for chronic tinnitus (Knipper et al., 2020). However, not all individuals experiencing hearing loss also develop tinnitus. Indeed, about 90 % of individuals with chronic tinnitus also experience hearing loss while only 30-40 % of hard of hearing individuals suffer from chronic tinnitus (Bhatt et al., 2016; Kim et al., 2025). Therefore, dissociating tinnitus from hearing loss is essential in hearing research – especially when investigating their underlying neural mechanisms (Elgoyhen et al., 2015).

1.1 Age-related hearing loss

The **degraded auditory input** in age-related hearing loss leads to difficulties in processing and understanding speech as many speech sounds are high-frequency sounds (Sprinzl & Riechelmann, 2010). Additionally, speech perception rarely occurs under perfect conditions and often involves background noise or multiple speakers which is particularly challenging for elderly and hard of hearing listeners (Wong et al., 2009, 2010).

Thus, age-related hearing loss is often associated with an increased **listening effort** (Matthen, 2016; Pichora-Fuller et al., 2016). Listening itself is defined as the process of hearing with intention and attention (Kiessling et al., 2003), whereas listening effort refers to the mental effort expended in demanding listening conditions, such as the allocation of attentional or cognitive resources in order to increase cognitive control and facilitate the listening process (Pichora-Fuller et al., 2016; Wingfield et al., 2005). As a consequence, the increase in listening effort may decrease available resources for other cognitive operations (Humes et al., 2013).

Recent research has already shown that there is a close relationship between speech-in-noise perception and **cognitive abilities** such as working memory (Arehart et al., 2013; Rönnberg et al., 2013; Souza & Arehart, 2015), episodic memory (Lin et al., 2011) cognitive flexibility (Shende et al., 2021) and inhibitory control (Shende et al., 2021; Shende & Mudar, 2023). Longitudinal studies further support the relationship between hearing loss and cognitive decline (Armstrong et al., 2020; Lin et al., 2011; Pronk et al., 2019). Several hypotheses have been formed in order to explain this link between age-related hearing loss and cognitive decline, however no single hypothesis has been proven to fully explain this link yet (for a review please read (Jafari et al., 2021)).

In adverse listening conditions, additional visual input can be beneficial and increase speech intelligibility (Wong et al., 2009, 2010). In hard of hearing participants in particular, reliance on the visual input facilitates speech perception (Moradi et al., 2016). However, there is also evidence that this increased influence by visual information can increase distraction by incongruent audiovisual motion stimuli (Puschmann et al., 2014). A paradigm that is often used to study **audiovisual integration** of speech sounds is the McGurk illusion, which can occur if the presentation of incongruent auditory and visual syllables (such as an auditory 'ba' and a visual 'ga') lead to the fused perception of a third syllable (such as 'da') (MacDonald & McGurk, 1978; McGurk & MacDonald, 1976). How often a person perceives the illusion is referred to as the McGurk susceptibility rate or the susceptibility to the McGurk illusion. A relationship between McGurk susceptibility and cross-modal activation in the auditory cortex has already been shown in cochlear implant patients (Stropahl et al., 2017).

Cross-modal plasticity – an increased neural response to stimuli in another modality – is often seen in the auditory cortex and even comprises Brodmann areas 41, 42 and 22. An increased neural activity during visual stimulation has been demonstrated in deafness (Allman et al., 2009; Lambertz et al., 2005; Lazard & Giraud, 2017; Lomber et al., 2010) but also in individuals with moderate age-related hearing loss (Campbell & Sharma, 2013, 2014). Functional magnetic resonance imaging (fMRI) studies further found changes in functional connectivity of the auditory cortex in response to audiovisual stimuli (Musacchia et al., 2009; Puschmann & Thiel, 2017).

In addition, an association between age-related hearing loss and **changes in brain structure** have been reported, such as a decrease in grey matter volume in the auditory cortex (Eckert et al., 2019; Qian et al., 2017) and an accelerated decline in whole-brain volume (Eckert et al., 2019; Peelle et al., 2011; Qian et al., 2017; Rigters et al., 2017). In addition, cortical thickness in the prefrontal cortex was positively related to speech perception in older adults (Giroud et al., 2018; Wong et al., 2010). Other studies using diffusion tensor imaging provided evidence of white matter integrity changes in age-related hearing loss covering longitudinal and fronto-occipital tracks (Husain et al., 2011; Luan et al., 2019) as well as language-related areas and auditory brain regions (Ma et al., 2016).

To conclude, there is evidence that hearing loss is associated with increased listening effort, decreased cognitive abilities, changes in audiovisual integration along with neuroanatomical and functional changes. However previous work was lacking studies on mild to moderate untreated age-related hearing loss. Further, the relationship between changes in behavior such as the increased listening effort and alterations in the brain was not investigated. Thus, the influence of the reduced auditory input and increased listening effort on neural mechanisms of audiovisual speech perception and cognitive processing in age-related hearing loss was largely unknown. Results of these investigations are of particular relevance as they advance our knowledge on neural changes associated with listening effort in hearing impairment. More importantly, the findings may have positive implications on treatment of hearing loss – such as hearing aid benefit.

As a consequence, several MRI studies with the focus on neural changes in age-related hearing loss have been carried out since 2016 that are presented as part of this habilitation thesis. The main aim was to investigate alterations in brain structure (grey and white matter; **Chapter 2.1**), neural activity (during auditory and audiovisual speech processing along with working memory paradigms; **Chapter 2.2**) as well as resting state functional connectivity (**Chapter 2.3**) in mild to moderate untreated age-related hearing loss. These results further motivated a hearing-aid fitting study to investigate whether changes in audiovisual integration and resting state functional connectivity are reversible by hearing-aid use (**Chapter 2.4**).

1.2 Tinnitus

The **perception of the tinnitus signal** significantly impacts quality of life and mental health in many tinnitus patients. General distress is increased and often comes with depression, anxiety and irritation but also problems in sleeping and concentration (Schecklmann et al., 2014). Unfortunately, no reliable treatment nor a cure is currently available.

Although the underlying **neural mechanisms** of tinnitus are largely unknown, there is compelling evidence that central auditory regions play a crucial role in tinnitus, but brain regions outside the auditory system, like prefrontal cortex and the limbic system, also contribute significantly to the tinnitus condition (Husain, 2016; Leaver et al., 2011, 2012, 2016; Rauschecker et al., 2010, 2015). It is most likely the connection between those areas that play a role in generating the tinnitus signal and most researchers have adopted the theory that tinnitus should be seen as a network problem (Dobel et al., 2023).

Moreover, tinnitus is often associated with **tinnitus-related distress** which is a multidimensional construct including psychological stress, sleep problems, negative thinking, impairments in concentration but also symptoms of anxiety, depression and affective symptoms (Brueggemann et al.,

2022). Importantly, the neural changes associated with chronic tinnitus are different from those that are associated with the experienced tinnitus-related distress. Prominent regions that are considered to play a role in tinnitus distress are the insula (Golm et al., 2013; Leaver et al., 2012; Liu et al., 2019), the amygdala (Husain, 2016), cingulate cortex (Besteher et al., 2019; Golm et al., 2013; Leaver et al., 2012) and frontal cortex (Golm et al., 2013; Han et al., 2018; Liu et al., 2019). Thus, there are different mechanisms behind the chronification of the tinnitus signal and the maintenance as well as annoyance with it.

Additionally, tinnitus is also associated with impairments in **cognitive functions** such as control of attention (Heeren et al., 2014; Mohamad et al., 2016; Tegg-Quinn et al., 2016; Trevis et al., 2016), inhibition (Araneda, De Volder, Deggouj, Philippot, et al., 2015; Araneda, De Volder, Deggouj, & Renier, 2015; Araneda et al., 2018; Brueggemann et al., 2021; Trevis et al., 2016) and general cognitive abilities such as short-term memory, working memory or concentration (Brueggemann et al., 2021; Mohamad et al., 2016; Wang et al., 2018). Further, tinnitus distress was shown to be a significant predictor of cognitive performance in tinnitus patients (Brueggemann et al., 2021). However, how cognitive abilities are associated with neural changes in chronic tinnitus remained to be investigated.

Even though the number of published articles on tinnitus and the general interest in it are steadily growing, its exact underlying pathophysiology is still under investigation. However, in order to advance treatment options, it is of utmost important to understand those underlying pathophysiological mechanisms. Furthermore, the interplay of the tinnitus perception, tinnitus distress, hearing loss and cognitive impairments complicates the understanding of the underlying mechanisms. Variability across studies regarding sample size, selection of control group, design of study and paradigm, imaging methodology as well as analysis methods lead to inconsistencies in findings across studies (Elgoyhen et al., 2015). Importantly, many studies lack appropriate control groups that are matched not only in age but also in hearing loss. Covariates such as tinnitus-related distress, anxiety and depression also need to be considered as confounds in previous studies, if these were not included in the analyses (Leaver et al., 2012, 2016).

Thus, I conducted neuroanatomical and functional MRI measurements in chronic tinnitus patients between 2020 and 2022 at Georgetown University. The three resulting publications are presented as part of this habilitation thesis. The aim of the studies was to investigate the neuroanatomical (**Chapter 2.5**) as well as functional changes (**Chapter 2.6**) in relation to the tinnitus perception itself as well as to the experienced tinnitus distress and cognitive functions in a well-controlled sample of participants (control participants were matched in age, gender and hearing loss).

The final chapter of the habilitation thesis will discuss how the published work significantly advanced current knowledge in the field and outline future research in age-related hearing loss (**Chapter 3.1**) and chronic tinnitus (**Chapter 3.2**). In order to draw final conclusions about both topics, general differences between age-related hearing loss and tinnitus will be compared (**Chapter 3.3**). For providing novel insights on neural mechanisms in age-related hearing loss and tinnitus, special attention will be payed to differences but also similarities in neural alterations of certain brain regions (**Chapter 3.4**). Even though hearing loss and tinnitus seem to be closely related, the summary will outline the crucial importance of differentiating the two in order to draw meaningful conclusions on underlying neural mechanisms (**Chapter 3.5**).

2. Results and Discussion of own publications

2.1 Brain structural alterations in hearing loss

On the basis of these publications:

- ***Rosemann, S.*** *& Thiel, C. M. (2020). Neuroanatomical changes associated with age-related hearing loss and listening effort. Brain Structure and Function, 225(9), 2689-2700. https://doi.org/10.1007/s00429-020-02148-w*
- ***Rosemann, S.*** *& Thiel, C. M. (2021). No association between age-related hearing loss and brain age derived from structural neuroimaging data. NeuroImage: Reports, 1(2), 100020. https://doi.org/10.1016/j.ynirp.2021.100020*

There is ample evidence regarding neuroanatomical differences between elderly hard of hearing and normal-hearing participants. However, previous studies were heterogeneous with respect selection of control groups (age-matched or not) and the sample size was rather low (n<20 participants). Further, the influence of the increased listening effort on alterations in brain structure has previously not been investigated.

Hence, we conducted the largest neuroimaging study with n=71 participants to explore the impact of untreated age-related hearing loss and listening effort on both grey and white matter changes in a well-matched sample of hard of hearing and normal-hearing participants. We acquired both anatomical MRI and diffusion-weighted MRI (DWI) scans to assess grey matter volume, cortical thickness and white matter integrity in all participants. This study demonstrated significant grey matter volume reductions in the middle frontal gyrus in hard of hearing compared to normal-hearing participants (**Rosemann & Thiel, 2020b**). Moreover, lower grey matter volume and cortical thickness in inferior frontal and orbitofrontal cortex were associated with higher daily life listening effort. Changes in white matter integrity (assessed by fractional anisotropy values) in relation to hearing loss or listening effort were not detected. We hereby presented the first neuroanatomical study in a large sample of age-related hearing loss that suggests that the decrease in hearing abilities is related to a loss of grey matter volume in frontal brain regions that are associated with speech perception. Further, cortical thinning and grey matter volume loss in orbitofrontal cortex are probably related to the conscious evaluation of the listening effort. We hereby demonstrated for the first time that neuroanatomical changes are related to the perceived daily life listening effort.

Further, we presented the first and largest study on the neuroimaging-derived brain age model in n=169 hard of hearing and normal-hearing elderly individuals (**Rosemann & Thiel, 2021**). For that aim, we determined the difference between chronological and brain-predicted age that was derived from the structural neuroimaging datasets. The true (chronological age) serves as a proxy for an aberrant ageing trajectory and is compared to the predicted brain age by using estimates of grey and white

matter. Our data did not suggest a significant correlation between accelerated brain-predicted age, age-related hearing loss or daily life listening effort. Thus, our results suggested that mild to moderate age-related hearing loss has negligible effects on brain age derived from structural neuroimaging data. Possible reasons are that the derived brain age model considers the whole brain and may not be a representative measure to capture structural alterations in age-related hearing loss that were mainly found in auditory and frontal brain regions or that our sample was too young and presented only mild to moderate decreases in hearing. Consequently, the question remains whether older age or more advanced stages of hearing loss are reflected in an accelerated brain predicted age.

To sum up, those neuroanatomical studies significantly advanced current knowledge of alterations in underlying brain structures in age-related hearing loss as we provided evidence for the first time that grey matter volume loss and cortical thinning in frontal cortex are associated with age-related hearing loss along with higher daily life listening effort. Hence, not only a decrease in hearing abilities but also behavioral outcome measures – such as the experienced daily life listening effort – are reflected in neuroanatomical changes in the frontal cortex. Contrary to our expectation, we found no evidence for changes in white matter structure or accelerated brain-predicted age. One may argue that untreated mild to moderate hearing loss may not significantly alter brain structure to a degree that may lead to detectable changes in white matter integrity or an accelerated brain-predicted age. Further, previous investigations included participants of up to the age of 88 and the majority of our sample was between the ages of 50 and 75. Consequently, it remains to be investigated whether more severe stages or longer durations of hearing loss (possibly with higher age of the participants) would be associated with more pronounced changes in brain structure. We conclude that there are only minimal structural changes in mild to moderate age-related hearing loss in total, but that important brain regions are in the frontal cortex. Determining those neuroanatomical mechanisms in age-related hearing loss may also serve as indicators for increased listening effort that may require hearing-aid treatment. Thus, future intervention studies offer valuable insights into how those neuroanatomical changes may be related to hearing-aid outcome by assessing whether those structural changes can be halted or even reversed.

2.2 Neural signatures of hearing loss assessed by task-based fMRI

On the basis of these publications:

- ***Rosemann, S.*** *& Thiel, C. M. (2018). Audio-visual speech processing in age-related hearing loss: stronger integration and increased frontal lobe recruitment, NeuroImage, 175, 425-437, https://doi.org/10.1016/j.neuroimage.2018.04.023*
- ***Rosemann, S.*** *& Thiel, C. M. (2020). Neural signatures of working memory in age-related hearing loss. Neuroscience, 429, 134-142, https://doi.org/10.1016/j.neuroscience.2019.12.046*
- ***Rosemann, S.,*** *Smith, D., Dewenter, M. & Thiel, C. M. (2020). Age-related hearing loss influences functional connectivity of auditory cortex for the McGurk illusion. Cortex, 129, 266-280, https://doi.org/10.1016/j.cortex.2020.04.022*
- *Pauquet, J., Thiel, C. M., Mathys, C. &* ***Rosemann, S.*** *(2021). Relationship between memory load and listening demands in age-related hearing impairment. Neural Plasticity, 2021, e8840452. https://doi.org/10.1155/2021/8840452*

Age-related hearing loss has widespread implications for speech perception, cognitive abilities such as working memory and attention switching, and the experienced effort to understand speech. However, the neural mechanisms underlying those behavioral changes was largely unknown. Thus, I conducted four fMRI experiments investigating neural processing of audiovisual speech, the McGurk illusion as well as visual and auditory working memory.

The first fMRI study investigated audiovisual speech processing in mild to moderate age-related hearing loss (**Rosemann & Thiel, 2018**). Twenty hard of hearing participants and nineteen age- and gender-matched normal-hearing participants performed two audiovisual speech tasks: one was a sentence detection task inside the MRI and the other one was the McGurk illusion task outside the MRI. Both tasks consisted of congruent and incongruent audiovisual conditions, as well as of auditory-only and visual-only conditions. In the sentence detection task, the incongruent condition involved presentation of two different sentences in the auditory and visual input. In the McGurk task, we had three different combinations: 1) auditory ‘ba’ / visual ‘ga’ (might lead to fused percept of ‘da’), 2) auditory ‘ba’ / visual ‘ta’ (might lead to fused percept of ‘da’) and auditory ‘pa’ / visual ‘ka’ (might lead to fused percept of ‘ta’). We found a significantly increased McGurk susceptibility in hard of hearing compared to normal-hearing participants. This McGurk susceptibility also significantly correlated with hearing loss indicating a higher illusion perception rate with higher hearing loss. Hence, we concluded that the influence of the visual input increases with severity of the hearing loss and therefore leads to higher audiovisual integration, i.e. increased McGurk susceptibility. Moreover, our fMRI results demonstrated an increased frontal lobe recruitment when processing incongruent audiovisual, auditory and visual speech in hard of hearing participants (Figure 1). This additional frontal activity was further modulated by the severity of hearing loss. We suggest, that this increased frontal activity may indicate increased listening effort in difficult speech understanding situations as it was not observed

when congruent audiovisual speech was presented. Interestingly, there were no differences between the two groups in the performance of the sentence detection task. This might suggest, that hard of hearing participants indeed tried harder to complete the task than their normal-hearing peers which may be reflected in the increased frontal activity. Hence, our study was the first to show that already mild to moderate untreated hearing loss is associated with altered neural activation during audio-visual speech processing particularly involving an additional recruitment of frontal brain regions.

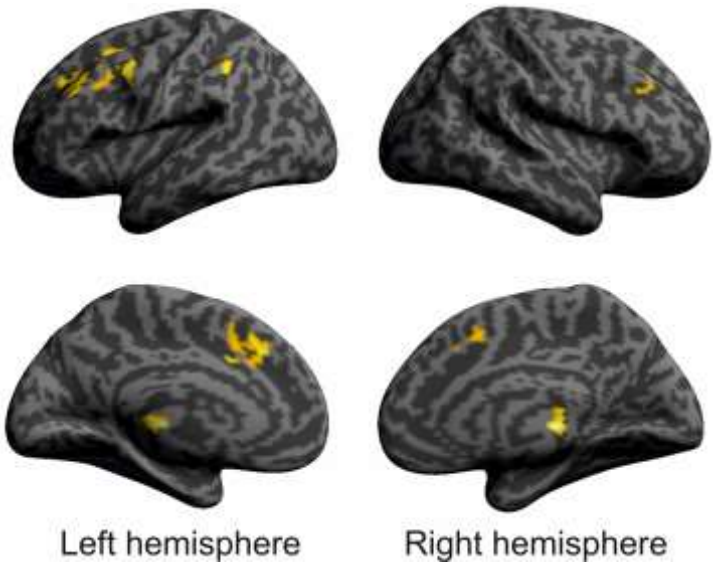

Figure 1: Increased frontal lobe activity during effortful speech perception in hard of hearing compared to normal-hearing participants (Figure created from results of Rosemann & Thiel, 2018)

Based on our findings of an increased McGurk susceptibility in age-related hearing loss, we conducted a follow-up study to investigate neural mechanisms of the McGurk illusion in twenty hard of hearing and twenty age- and gender-matched normal-hearing participants (**Rosemann et al., 2020**). The paradigm was a continuous scanning paradigm with audiovisual congruent, audiovisual incongruent (McGurk), auditory-only and visual-only conditions. Here, we only used the combination of auditory ‘ba’ / visual ‘ga’ (might lead to fused percept of ‘da’), since this has shown to work best for German native speakers (based on the results of the previous publication). The McGurk susceptibility was equally high in both groups (probably because of the continuous scanning) and correlated with speech-in-noise perception and daily life listening effort. Neural activity patterns were not significantly different between the two groups, but task-modulated functional connectivity between auditory, visual, parietal and frontal areas was significantly higher in the hard of hearing participants when comparing McGurk versus congruent audiovisual stimuli. This increased connectivity may be an adaptive mechanism for daily speech conversation, in which the auditory input is decreased due to the hearing loss and hence visual input such as lip movement, can facilitate the perception of speech. Thus,

we showed that under adverse listening conditions (such as with scanner noise), the susceptibility of the McGurk illusion is associated with speech-in-noise perception and daily life listening effort. Further, our study was the first to provide evidence that already mild to moderate age-related hearing loss is linked to altered functional connectivity of the auditory cortex when processing McGurk compared to congruent audiovisual input. We hereby demonstrated that hard of hearing participants might have different processing strategies even though behavioral outcome measures – in this case the McGurk illusion rate – were similar across normal hearing and hard of hearing individuals. Therefore, these results significantly advance our knowledge on neural changes in age-related hearing loss that may also play a crucial role in hearing aid treatment.

Previous research has shown that there is a close relationship between the decrease in hearing abilities and cognitive decline. In addition, executive functions – for instance cognitive flexibility and working memory – have been associated with speech perception abilities. Less clear have been the neural implications of these compensatory efforts. Specifically, it was unclear whether mild to moderate uncompensated hearing loss has consequences on prefrontal functions during cognitive processing. Hence, we carried out two working memory studies. The first study used a visual working memory paradigm (**Rosemann & Thiel, 2020a**) based on a previous study in deaf individuals who showed weaker recruitment of frontal brain regions. We additionally explored the relationship between speech-in-noise perception and cognitive abilities such as working memory, cognitive flexibility and inhibition control. Nineteen normal-hearing and nineteen hard of hearing participants took part in the study. The working memory paradigm was a two-back task with images of faces and houses (separate conditions). The control condition was a zero-back condition with two target stimuli (one famous face and one famous building). However, our results showed no significant differences in frontal brain activation patterns and working memory performance between hard of hearing individuals and their normal-hearing peers in any of the conditions. The behavioral data demonstrated evidence of decreased cognitive flexibility in hard of hearing participants. The additional regression analysis revealed that hearing loss and cognitive flexibility were significant predictors of speech-in-noise perception in the hard of hearing group. We hereby presented the first study on neural mechanisms of visual working memory in mild to moderate age-related hearing loss and concluded that both behavioral and neural correlates of visual working memory are intact but that cognitive flexibility may be already impaired in mild to moderate age-related hearing loss.

Our second working memory study was the first investigating verbal working memory in the context of a sentence processing task in age-related hearing loss (**Pauquet et al., 2021**). As hearing loss is associated both with decline in cognitive abilities along with decreased speech perception, we here investigated n=19 normal-hearing and n=20 hard of hearing participants using an fMRI paradigm that varied both the listening condition as well as the memory load. In all conditions, two sentences were

presented. In the low memory condition, one word from the second sentence had to be detected while in the high memory load condition participants had to indicate whether the noun or verb was the same in both sentences (we asked for either verb or noun). Additionally, sentences were presented at two different sound intensity levels based on the participants' speech reception threshold (80% intelligibility level). The difficult listening condition was the one with 80% intelligibility and in the easy condition 5dB was added to that sound level for each participant. Surprisingly, we found an interaction effect of memory load and listening condition on the behavioral level that was not reflected in brain activation patterns. We only found a significant effect of memory load indicating increased activity in supramarginal gyrus, middle frontal gyrus and supplementary motor cortex in all participants. Neural activity in this experiment was not associated with mild to moderate age-related hearing loss. A possible explanation for the absent effect of listening condition may be that listening conditions were not distinct enough to detect neural differences. Future studies may further benefit from a sparse-sampling design to allow varying speech intelligibility levels by adding speech noise (and not by varying the sound intensity level of the speech combined with stationary noise of the MRI). Possible explanations for the absence of group effects may be that the mild to moderate hearing loss may not have been advanced enough which means that additional recruitment in the verbal memory task was not needed or that the task was difficult in general and hence led to equally increased brain activity in both groups.

In sum, those studies demonstrated that neural activity is not necessarily different in hard of hearing participants compared to their normal-hearing peers. Our sentence detection task showed an increased frontal lobe recruitment in difficult listening situations and we found increased functional connectivity of the auditory cortex in McGurk conditions. On the other hand, visual and verbal working memory paradigms did not show differences between groups. Thus, it seems that neural signatures of cognitive processes are intact in mild to moderate age-related hearing loss. Those results are of particular relevance to advance our current knowledge on cognitive and neural implications of age-related hearing loss that may be especially relevant for hearing aid treatment.

2.3 Changes in resting state functional connectivity in hearing loss

On the basis of these publications:

- ***Rosemann, S.*** *& Thiel, C. M. (2019). The effect of age-related hearing loss and listening effort on resting state connectivity. Scientific Reports, 9:2337. doi: 10.1038/s41598-019-38816-z*
- *Schulte, A., Thiel, C. M., Gieseler, A., Tahden, M., Colonius, H. &* ***Rosemann, S.****, (2020). Reduced Resting State Functional Connectivity with Increasing Age-Related Hearing Loss and McGurk Susceptibility. Scientific Reports, 10:16987. https://doi.org/10.1038/s41598-020-74012-0*

In addition to functional activity and connectivity during various tasks, we assessed changes in resting state functional connectivity in age-related hearing loss. The term resting state functional connectivity refers to the spontaneous activity that is organized into coherent networks such as the default mode, the dorsal attention or salience network (Husain et al., 2014). Previous literature provides evidence for changes in resting state functional connectivity changes in age-related hearing loss, however, the picture is not coherent. Further, how the increased listening effort adds to those functional changes has been an unresolved issue. In two resting state fMRI studies we therefore investigated how uncompensated age-related hearing loss, listening effort as well as audiovisual abilities relate to functional connectivity at rest.

Hence, we investigated the influence of age-related hearing loss and daily life listening effort on resting state functional connectivity in n=19 hard of hearing and n=19 age- and gender-matched normal-hearing participants. The results demonstrated that daily life listening effort but not the hearing loss itself was related to decreased resting state functional connectivity in various areas, for instance between the dorsal attention network to the precuneus and to superior parietal lobule as well as between auditory and fontal cortex (**Rosemann & Thiel, 2019**). In other words, an increase in the experienced daily life listening effort was associated with lower resting-state functional connectivity. We hereby demonstrated for the first time, that behavioral outcomes of the degraded auditory input – such as the increased daily life listening effort – are associated with changes in resting state functional connectivity.

Additionally, we investigated the relationship of the susceptibility to the McGurk illusion and resting state functional connectivity in a large sample of n=65 elderly participants with varying degree of age-related hearing loss including normal hearing to severe hearing loss. Here, we found decreased functional coupling between several resting state networks, covering the salience and dorsal attention networks **(Schulte et al., 2020**). Specifically, increased age-related hearing loss was associated with decreased functional connectivity of the salience network to the cuneal cortex and of the dorsal attention network to an area in the pre/postcentral gyrus along with the cerebellum. Moreover, we found reduced coupling of the auditory cortex to the pre- and postcentral gyrus as well as between

the M1 lip area and the planum temporale with an increased susceptibility of the McGurk illusion. In sum, we demonstrated for the first time that a decrease in functional coupling is associated with increased hearing loss and an increased susceptibility to the McGurk illusion. We hereby provided further support that not only the decrease in hearing abilities but also the associated consequences – for instance daily life listening effort or McGurk illusion susceptibility – are related to alterations in resting state functional connectivity.

Hence, both studies provide evidence for decreased resting-state functional connectivity of various brain regions such as dorsal attention network and auditory cortex with increasing hearing loss and listening effort. Additionally, functional coupling of auditory and somatosensory cortices was correlated with McGurk illusion susceptibility. It seems that functional coupling of these brain areas is disrupted already in mild to moderate age-related hearing loss. Possible explanations may be a general coupling deficiency of the aforementioned networks or a compensatory downregulation of functional connectivity due to the situation at rest which does not require any effortful task. We suggest, that there is an increase in connectivity between relevant brain areas (such as auditory cortex and frontal areas) during effortful speech processing or audiovisual integration (based on results from functional connectivity changes during the McGurk illusion as described in chapter 2.2) which is reversed into a diminished functional coupling at rest. In other words, the decreased resting-state functional connectivity may be a sign of a compensatory mechanism for the enhanced co-activation during task performance.

Age-related hearing loss and its associated increase in experienced daily life listening effort along with the susceptibility to the McGurk illusion seem to be associated with an overall decline of functional resting state coupling affecting different brain areas and networks. Interestingly, the functional coupling of the auditory cortex seems not to be changed in relation to the hearing loss but rather to the consequences of it (such as listening effort or McGurk susceptibility). On the other hand, the degree of hearing loss is correlated to resting state functional connectivity of certain networks, for instance the dorsal attention network, starting already at early stages of hearing loss. Hence, not only the hearing loss itself, but also the associated changes in experienced listening effort and susceptibility to the McGurk illusion are reflected in altered resting state functional connectivity of various brain regions already at early stages of hearing loss.

2.4 The influence of hearing aid fitting on functional connectivity

On the basis of this publication:

- ***Rosemann, S.**, Gieseler, A., Tahden, M., Colonius, H. & Thiel, C. M. (2021). Treatment of age-related hearing loss alters audiovisual integration and resting-state functional connectivity: A randomized controlled pilot trial, ENeuro. https://doi.org/10.1523/ENEURO.0258-21.2021*

The previously described studies demonstrated that untreated age-related hearing loss is associated with an increase in audiovisual integration and decreases in resting state functional connectivity. One of the primary treatments for age-related hearing loss is the amplification of the auditory input through hearing aids. Wearing hearing aids is linked to self-reported improvements in communication based on the increased speech clarity (Karawani et al., 2018), improvements in perceiving speech along with decreased experienced listening effort (Sarant et al., 2020). Thus, there is a growing interest on the beneficial effects of hearing aid use on neural and behavioral outcomes in age-related hearing loss (Amieva & Ouvrard, 2020; Lin et al., 2011). In particular, it is currently not known whether and how amplification of the auditory input by hearing aids influences audiovisual integration and resting state functional connectivity. However, randomized controlled studies with hearing aid fittings are scarce.

We conducted a pilot randomized controlled hearing aid fitting study with 32 hard of hearing participants (**Rosemann et al., 2021**). Half of them were measured one week before and six months after the first fitting of a hearing aid (treatment group). The other 16 participants were not fitted with a hearing aid and were measured twice at an interval of six months as well (waiting control group). Our results suggested that hearing aid fitting impacts resting state functional connectivity between auditory and visual regions as well as audiovisual integration abilities assessed with the McGurk illusion. Specifically, functional connectivity between the auditory cortex and fusiform gyrus was significantly decreased in the treatment group while no significant change was obtained in the control group (Figure 2). Additionally, there was an increase in the McGurk illusion after 6 months of hearing aid use which was also significantly correlated to the decrease in functional connectivity (Figure 2). This increase in McGurk susceptibility rate was also associated with a decreased hearing aid benefit in auditory-only speech-in-noise perception. In other words, hearing aid use of six months potentially increases the reliability of the auditory input leading to better speech-in-noise perception and lower McGurk illusions. However, those participants with worse speech-in-noise perception and higher McGurk illusion showed less hearing aid benefit probably because of a less reliable auditory input.

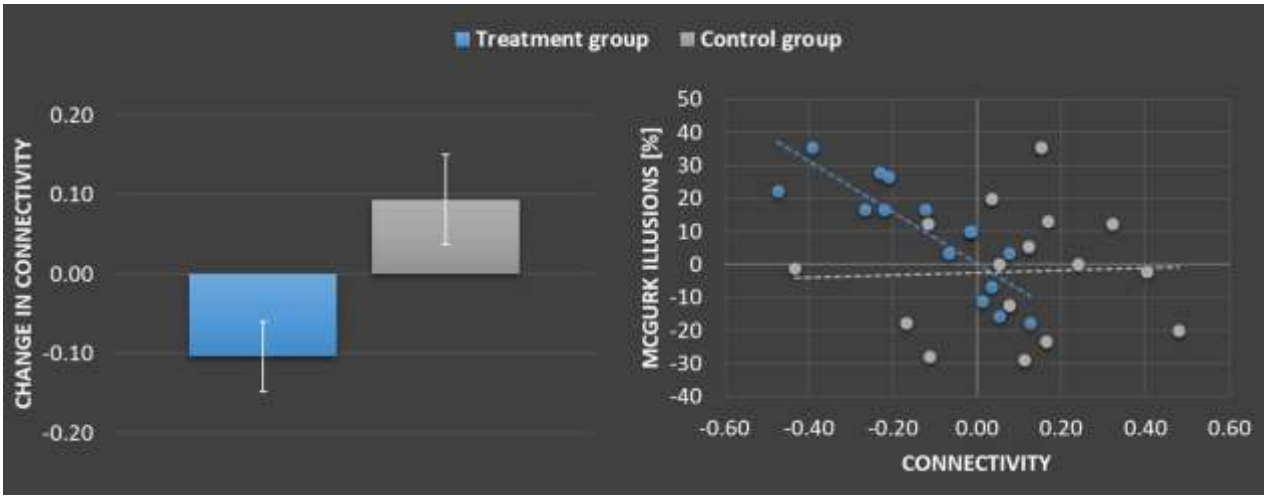

Figure 2: left: Change in resting state functional connectivity of the auditory cortex to fusiform gyrus between the measurements at baseline and after six months for the treatment (blue) and control (grey) group. Negative values refer to a decrease in connectivity between the respective regions after six months, positive values refer to an increase in connectivity after six months.
right: Relationship between change in functional connectivity and the change in McGurk illusion rate. (Figure created from results of Rosemann et al., 2021)

Hence, this study demonstrated that changes in functional connectivity and audiovisual integration can already be seen after a relatively short period of hearing aid use. Moreover, we were able to show that an increased influence of visual input on the McGurk illusion perception seems to inhibit the beneficial effect of hearing aid use (in the auditory condition only). Thus, our results also suggest that alterations in audiovisual integration, i.e. McGurk illusion perception, may be relevant for speech comprehension and communication in everyday life.

However, based on a few limitations, for instance the fact the treatment group was only tested in unaided conditions and the lack of power due to the low sample size, this study can only be seen as a pilot study. Nevertheless, we are confident that the presented results may trigger future research on the effects of hearing aid fitting in age-related hearing loss considering larger sample sizes, long-term use of hearing aids and the assessment in aided and unaided conditions.

2.5 Alterations in brain structure in tinnitus

On the basis of these publications:

- ***Rosemann, S.**, & Rauschecker, J. P. (2022). Neuroanatomical alterations in middle frontal gyrus and the precuneus related to tinnitus and tinnitus distress. Hearing Research, 108595. https://doi.org/10.1016/j.heares.2022.108595*
- ***Rosemann, S.,** & Rauschecker, J. P. (2023). Increased fiber density of the fornix in patients with chronic tinnitus revealed by diffusion-weighted MRI. Front. Neurosci. 17:1293133. https://doi.org/10.3389/fnins.2023.1293133*

There is compelling evidence that not only central auditory regions but also other brain areas play a crucial role in tinnitus. Previous studies demonstrated various differences in grey matter volume, cortical thickness and measures of white matter integrity. However, these brain morphological studies show an inconsistent picture, probably because of heterogeneous patient groups and selection of control groups that were not matched in age or hearing loss. Hence, it is not clear which underlying anatomical changes relate to increasing age, hearing impairment, or solely to the development of chronic tinnitus. Furthermore, it has been shown that chronic tinnitus is associated with cognitive impairments, but their relationship to alterations in brain structure has not been investigated yet.

We investigated neuroanatomical alterations related to the tinnitus perception itself along with tinnitus distress and cognitive abilities in 20 tinnitus patients and 20 age-, gender- and hearing loss matched control participants. Our first study showed higher grey matter volume in the middle frontal gyrus in tinnitus patients compared to control participants **(Rosemann & Rauschecker, 2022**). Additionally, the results demonstrated increased cortical thickness in the precuneus associated with tinnitus distress in the tinnitus group (Figure 3). Lastly, we found a group interaction between cognitive assessment scores and cortical thickness of the middle frontal gyrus, showing higher cortical thickness with better scores in controls and lower scores in tinnitus patients. Hence, we found that brain structure of the precuneus is related to tinnitus distress while frontal brain regions contribute to associations with the tinnitus perception itself along with cognitive abilities. We hereby presented the first study providing evidence for a relation of neuroanatomical changes and cognitive abilities in chronic tinnitus.

In our second study we investigated white matter morphology using diffusion-weighted MRI and used a fixel-based approach to resolve the multiple fibers problem (**Rosemann & Rauschecker, 2023b**). Usually one voxel contains multiple and sometimes even crossing white matter tracts – denoted as fiber population. Standard models (for instance diffusion tensor modeling) cannot capture multiple fibers within a voxel. A fixel-based analysis, in contrast, enables the analysis of specific fiber pathways even in regions containing crossing fibers. Hence, the main aim of a fixel-based analysis is to investigate

whether alterations in intra-axonal volume are related to decreased fiber density (microstructure) or reduced fiber bundle cross section (macrostructure). Our study provided evidence of a significantly higher fiber density in the fornix in tinnitus patients compared to control participants.

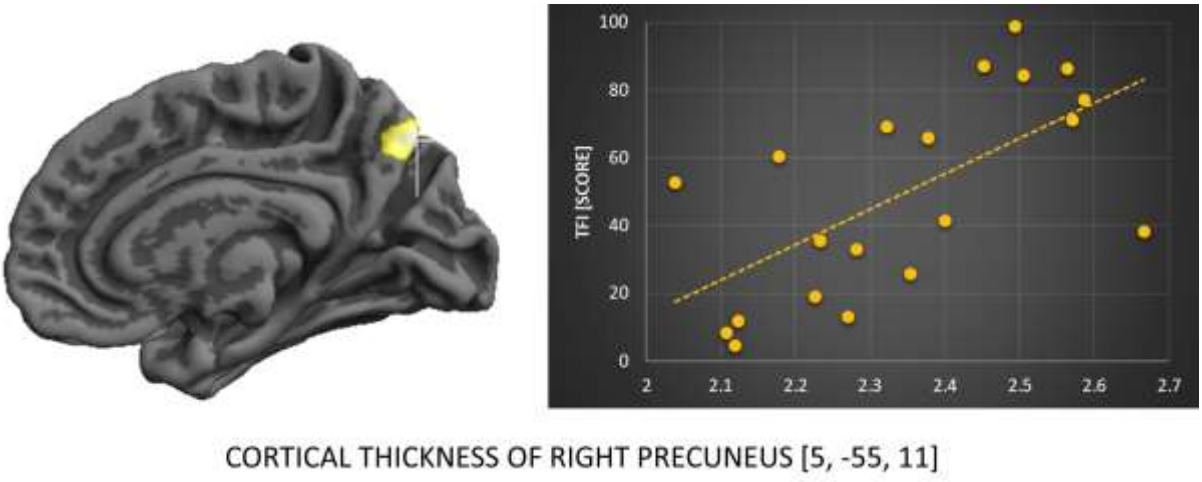

Figure 3: Significant correlation between cortical thickness of the precuneus (shown on the left) and tinnitus distress determined by Tinnitus Functional Index (TFI) scores in the tinnitus group (Figure created from results of Rosemann & Rauschecker, 2022)

Hence, our findings demonstrated significant differences in brain structure between tinnitus patients and control participants that showed higher grey matter volume in the middle frontal gyrus and higher fiber density in the fornix in tinnitus patients. In addition, we found increased cortical thickness in the precuneus associated with tinnitus distress as well as a different association of cognitive scores and cortical thickness in the middle frontal gyrus in tinnitus patients and control participants.

We suggest that the increased grey matter volume and fiber density in tinnitus patients reflect either a compensatory mechanism related to the negative emotional processing of the tinnitus signal or a maladaptive mechanism indicating higher symptomatology due to a reinforced learning of the tinnitus signal. In addition, we argue that the increased awareness and annoyance of the tinnitus signal is reflected in the increased cortical thickness of the precuneus. Thus, this may indicate a compensatory alteration which is due to the constant attempt to attenuate and ignore the tinnitus signal. Additionally, these compensatory mechanisms may also interfere with cognitive abilities. We hypothesize that the middle frontal gyrus may be recruited in tinnitus patients to increase cognitive control to attenuate the tinnitus signal and that this may interfere with cognitive resources available for other cognitive tasks.

2.6 Functional changes in relation to cognition in tinnitus

On the basis of this publication:

- ***Rosemann, S.,*** *& Rauschecker, J. P. (2023). Disruptions of default mode network and precuneus connectivity associated with cognitive dysfunctions in tinnitus. Scientific Reports 13, 5746. https://doi.org/10.1038/s41598-023-32599*

In addition to the aforementioned structural changes in chronic tinnitus, we were also interested in alterations in resting state functional connectivity associated with the tinnitus perception, the experienced tinnitus distress as well as cognitive abilities. Previous resting state functional connectivity studies presented a rather heterogeneous picture suggesting that an interaction of multiple brain regions and networks are involved in the tinnitus perception itself and differently relate to tinnitus distress. However, the relation between changes in functional connectivity and cognitive abilities in chronic tinnitus still needed to be addressed.

For that aim, we conducted a resting state functional connectivity study in twenty tinnitus patients and twenty control participants (**Rosemann & Rauschecker, 2023a**). Even though we did not obtain significant differences in resting state functional connectivity between the two groups, our results demonstrated that tinnitus distress correlated with resting state functional connectivity between the precuneus and the lateral occipital complex. Additionally, we found significant associations between general cognitive abilities and resting state functional coupling of various brain regions, such as the default mode network and the precuneus with a) the superior parietal lobule, b) the orbital cortex and c) the supramarginal gyrus. In detail, it seems that lower cognitive scores were correlated with negative connectivity values (anticorrelation), while higher scores (indicative of normal cognitive function) were correlated with positive connectivity values.

Contrary to our expectation, we did not obtain significant differences in functional coupling between tinnitus patients and control participants. Possible reasons for the absent group differences that have been shown by various other researchers may be different resting state acquisition (eyes-open versus eyes-closed paradigms), different analysis methods and seed regions, higher number of participants and differences in participant selection (both tinnitus patients as well as control groups that were or were not matched in age and hearing loss). For future studies it may be beneficial to use similar acquisition paradigms, seed regions and analysis methods across studies to allow comparability and increase reproducibility.

The positive relationship between tinnitus distress and resting-state functional connectivity between the precuneus and the lateral occipital cortex could be a sign of cross-modal plasticity (similar to that seen in deaf or blind patients) attempting to reduce the gain of the tinnitus sensation. In that case, visual brain regions may be responding to the internal sensation of the tinnitus signal by trying to

reduce involuntary attention to it. Cross-modal effects are most likely an effect of the tinnitus (and its experienced distress) rather than a cause of it and have been shown by various other researchers as well. Hence, visual areas may also serve as potential target areas for interventions, for instance neuromodulatory therapies.

Importantly, we hereby present the first study providing evidence of disruptions of default mode network and precuneus coupling that are related to cognitive dysfunctions in chronic tinnitus. The orbitofrontal cortex, the superior parietal lobule and the supramarginal gyrus are thought to be engaged in compensatory processes related to the annoyance by the tinnitus signal. Hence, we argue that disruptions of resting state functional connectivity are associated to cognitive abilities in tinnitus, because the affected areas are involved in attenuating the tinnitus signal. Thus, those resources are already occupied and not available for concurrent cognitive tasks. The present findings provide novel insights into neural mechanisms in tinnitus patients related to cognitive functions and stress the importance of including assessments of cognitive abilities in tinnitus research.

3. Conclusion and Outlook

3.1 Age-related hearing loss

Age-related hearing loss is a common disorder in the aging population which affects speech understanding, particularly under adverse listening situations. Consequently, successful communication may be impaired which may lead to social isolation and loneliness. Further, age-related hearing loss is often accompanied by cognitive decline and it is also one major risk factor for dementia. Thus, research on cognitive and neural implications of age-related hearing loss is highly important.

My work has demonstrated grey matter volume loss and cortical thinning in frontal cortex associated with age-related hearing loss and increased daily life listening effort. We did not find alterations in white matter structure or accelerated brain-predicted age. Thus, we concluded that mild to moderate age-related hearing loss only leads to minimal structural changes, but that those changes are seen in frontal brain regions. In contrast, we presented evidence of neural changes in response to audiovisual speech and the McGurk illusion. We showed additional frontal lobe recruitment in difficult listening conditions and an increased task-modulated functional connectivity of the auditory cortex in response to the McGurk illusion in hard of hearing participants. No changes in neural signatures of visual or verbal working memory were observed in age-related hearing loss. In sum, we suggest that neural changes are observed in age-related hearing loss dependent on the task. If speech material is presented (such as sentences) and listening conditions are difficult, additional frontal regions may be recruited as means of the increased listening effort. Increased auditory cortex coupling was observed during presentation of McGurk syllables (i.e. incongruent audiovisual input). Signatures of cognitive processes such as visual or verbal working memory seem not to be affected in mild to moderate declines in hearing. Thus, it may be the perceptual part that is related to functional neural changes and not the cognitive part. Interestingly, age-related hearing loss and associated changes in daily life listening effort and the susceptibility to the McGurk illusion were reflected in wide-spread changes in resting state functional connectivity covering auditory cortex, somatosensory cortex, salience and dorsal attention networks. Important is that functional connectivity of the auditory cortex seems not to be associated with the decline in hearing itself but rather to the consequences of it, such as the increased listening effort. In sum, mild to moderate degrees of hearing loss are associated with profound alterations in the resting brain which is probably an indication of a long lasting compensatory mechanism early in the course of hearing loss. We further extend this assumption by showing that even a short period of wearing a hearing aid (six months) is associated with changes in resting state functional connectivity as well as the susceptibility of the McGurk illusion. These results indicate that some of the changes in age-related hearing loss are reversible by hearing aid treatment.

The present findings of changes in neural activity and connectivity related to speech processing, McGurk illusion perception as well as during resting state along with the pilot study on hearing-aid fitting provided novel insights into changes of audiovisual integration and functional connectivity that are potentially affected by short term hearing aid use of 6 months. However, how neural mechanisms of the McGurk illusion are affected by hearing aid treatment was not investigated so far. Hence, the previous results paved the way for a subsequent large scale hearing aid fitting study that investigates how these neural alterations are affected by hearing-aid treatment of 10-12 months. Data collection for this study is currently ongoing and involves a McGurk task, a continuous speech paradigm and a resting state measurement in order to assess changes in neural activity as well as connectivity in response to rest, audiovisual integration and audiovisual speech processing. Hence, this study also allows to draw conclusions on changes in neural activity during different tasks after hearing aid use.

Moreover, my research highlighted that also behavioral outcomes of the degraded auditory input – such as the increased daily life listening effort – are related to changes in neural mechanisms in age-related hearing loss. Thus, the increase in listening effort may decrease available resources for other cognitive operations (Humes et al., 2013). Therefore, the assessment of listening effort offers insights into the interaction of 'bottom-up' (sensory and in this case auditory) processing and 'top-down' mechanisms (working memory, attention and concentration) and may serve as a more sensitive marker of neural alterations than hearing abilities determined by pure-tone audiometry (Bernarding et al., 2017; Naylor et al., 2018; Pichora-Fuller et al., 2016). These findings are therefore highly relevant for hearing aid treatment as the goal of hearing aid fitting should go beyond simply restoring the auditory input and consider reducing the individual's listening effort (Pichora-Fuller et al., 2016).

Previous research has shown that the peak pupil dilation is as a sensitive and reliable psychophysical measure of listening effort that is sensitive to interindividual characteristics such as hearing loss (Zekveld et al., 2010, 2011). However, the results in hard of hearing individuals are inconsistent. Measuring the pupil size is non-invasive and can easily be combined with the presentation of auditory stimuli (for instance speech intelligibility tests). Hence, it may be a useful tool in hearing aid fitting to determine not only whether speech intelligibility improved but also whether the listening effort decreased or not. In order to advance hearing aid fitting and establish this method for clinical purposes, the association between pupil size and neural activity in age-related hearing loss needs to be clarified. For that aim, I am conducting a simultaneous fMRI and pupillometry study to assess how listening effort is reflected in neural activity and pupil diameter in age-related hearing loss. Results of this study are of particular relevance as they advance our knowledge on neural changes associated with listening effort in hearing impairment. Moreover, the findings may aid in determining the clinical relevance of the pupil dilation response in age-related hearing loss as an objective marker of listening effort.

Even though we only found minimal structural changes in age-related hearing loss, research in aging has demonstrated neurotransmitter concentration changes in the auditory cortex (Lalwani et al., 2019) along with changes in microstructural measures that covered demyelination in frontal, temporal and parietal brain regions (Callaghan et al., 2014; Draganski et al., 2011; Karolis et al., 2019) and increased iron accumulation in subcortical brain areas, the cingulate and prefrontal cortex (Lorio et al., 2014; Pirpamer et al., 2016; Ward et al., 2014). However, the influence of age-related hearing loss and the experienced daily life listening effort of those measures has not been investigated so far. Hence, I am currently also using different MRI techniques such as MR-spectroscopy and quantitative MRI in order to explore alterations in neurotransmitter concentrations in the auditory cortex as well as consequences of age-related hearing loss on demyelination and iron accumulation. In order to advance treatment options for age-related hearing loss such as optimizing hearing-aid fitting or determining whether certain neurotransmitter systems may serve as potential treatment targets, understanding the complex underlying neural changes is of crucial importance.

To summarize, the presented studies provided valuable insights into alterations of structural and functional changes in mild to moderate age-related hearing loss. Important brain regions are the frontal cortex, auditory cortex and several resting state networks such as the dorsal attention network. One suggestion for future studies may be to investigate changes in more severe stages or longer durations of hearing loss. Age-related hearing loss is gradual, slowly progressing and often remains undiscovered for several years. Therefore, assessing the impact of the duration of hearing loss is a challenging although important endeavor. In addition, future studies should employ longitudinal approaches to investigate how structural and neural changes progress in age-related hearing loss and whether they can be halted or even be reversed by hearing-aid treatment.

3.2 Tinnitus

Hair cell damage followed by hearing impairment due to age-related hearing loss but also loud noise exposure is one of the peripheral causes for tinnitus. Chronic tinnitus has a significant impact on quality of life and mental health and is often accompanied by distress, fatigue, depression, anxiety and problems in sleeping and concentration. Unfortunately, there is currently no effective treatment or even a cure for tinnitus and in order to advance treatment options, it is of utmost importance to understand its underlying pathophysiology. However, even though the number of published articles on tinnitus and the general interest is steadily growing, the exact mechanisms of tinnitus are still under investigation.

My work provided evidence of higher brain volume in frontal cortex along with higher fiber density in the fornix in tinnitus patients compared to control participants. Those structural changes possibly

reflect either a compensatory mechanism related to the negative emotional processing of the tinnitus signal or a maladaptive mechanism indicating higher symptomatology due to a reinforced learning of the tinnitus signal. We further showed that tinnitus distress is associated with increased cortical thickness as well as an increased resting state functional connectivity of the precuneus. We think that those structural and functional changes are a reflection of the increased awareness and annoyance of the tinnitus signal and that this may indicate a compensatory alteration which is due to the constant attempt to attenuate and ignore the tinnitus signal. Those findings highlight the role of the precuneus in chronic tinnitus, strengthening its role specifically in the associated tinnitus distress. Moreover, these compensatory mechanisms may also interfere with cognitive abilities. We found that cognitive scores were differently associated in tinnitus patients and control participants indicating a negative correlation between cortical thickness in frontal cortex and lower scores in chronic tinnitus whereas a positive correlation was obtained in the control group. We extended those findings by showing a specific relationship between resting state functional connectivity of the precuneus and the default mode network and cognitive abilities that was not present in control participants. Here, it seemed that lower cognitive scores were correlated with negative connectivity values (anticorrelation), while higher scores (indicative of normal cognitive function) were correlated with positive connectivity values. We suggest that the relationship between cognitive scores and structural as well as functional alterations indicates that those areas are recruited to increase cognitive control to attenuate the tinnitus signal and that this may interfere with cognitive resources available for concurrent cognitive tasks. Therefore, the present findings provide novel insights into neural mechanisms in tinnitus patients related to cognitive functions and stress the importance of including assessments of cognitive abilities in tinnitus research.

Importantly, those findings motivated another study that is currently ongoing and investigates a full range of cognitive abilities (including working memory, attention and inhibitory control) in chronic tinnitus patients to allow for a more detailed clinical profile. In addition, we here focus on possible impairments in speech-in-noise perception as well as increases in experienced daily life listening effort. The final aim of this study is to assess the relationship between hearing related measures and cognitive abilities as well as their possible relation to the experienced tinnitus distress. Hopefully, the study will also pave the way for further research assessing neural alterations during different cognitive tasks in chronic tinnitus.

To sum up, the presented studies provided valuable insights into alterations of structural and functional changes in chronic tinnitus as well as their relation to tinnitus distress and cognitive abilities. Important brain regions are the frontal cortex, the fornix, the precuneus and the default mode network. The key in advancing treatment options for tinnitus and evaluating the efficacy of tinnitus interventions lies in understanding its underlying pathophysiology. Importantly, our results were not

confounded by age or hearing loss and may trigger future research investigating neural changes in chronic tinnitus and their association to the experienced tinnitus distress along with cognitive abilities. However, it is not clear whether the presented changes contribute to the onset of tinnitus or whether they are a result of the chronic tinnitus sensation. It is difficult to answer this question solely on the basis of correlational analyses. Most likely those associations can be seen as a result of the tinnitus rather than the cause because the participating tinnitus patients already had tinnitus for a longer time period. Thus, longitudinal studies may aid in making inferences about causality of neural alterations in chronic tinnitus and in capturing changes over time.

3.3 More profound changes in tinnitus than hearing loss

The here presented investigations about neural changes in age-related hearing loss and tinnitus seem to indicate that there are more profound alterations in brain structure and function in chronic tinnitus compared to hearing loss (alone). In mild to moderate age-related hearing loss we mostly identified altered functional connectivity and in some cases changes in neural activity. Structural changes were seen in grey matter volume and cortical thickness only. In contrast, we found changes in grey and white matter as well as altered functional resting state coupling in chronic tinnitus.

One possible reason for more profound changes in tinnitus may be that the onset is usually more sudden (and can often be remembered well) whereas the decrease in hearing in age-related hearing loss is slow and gradual. Hence, the brain can slowly adapt to (and possibly compensate for) the gradually decreasing hearing abilities which may therefore be unnoticed for quite some time. Importantly, only small changes need to be compensated for, since there is not a drastic loss of hearing in age-related hearing loss from day to day. In chronic tinnitus the onset is sudden and sometimes even associated with a specific event (such as loud noise exposure). In this case, the brain has to adapt to a much bigger change in hearing on the one hand and to the perception of the tinnitus signal on the other hand. These compensatory mechanisms probably need to be much stronger since the change in sensation is also much stronger (from not perceiving to perceiving the tinnitus and from no hearing loss to hearing loss). Additionally, hearing loss usually *precedes* tinnitus: there can be a longer duration in case of age-related hearing loss that at some point may be accompanied by the perception of tinnitus or a relatively short to no period of hearing loss before the onset of tinnitus usually seen after loud noise trauma or sudden hearing loss. Interesting although difficult may be to investigate the neural changes over time of periods where only hearing loss was present to the status where hearing loss and tinnitus are present.

Another reason for the widespread changes in brain structure and function in chronic tinnitus may be the increased burden of tinnitus which seems to be experienced as much more debilitating than in

hearing loss. Age-related hearing loss is associated with difficulties in understanding speech and increased listening effort, which potentially may lead to social isolation and loneliness if not treated by a hearing aid or cochlear implant (Cardin, 2016; Lin, 2012). Chronic tinnitus adds the constant auditory disturbance by the perception of the tinnitus signal which might lead to problems in concentration, sleeping disorders, stress, anxiety and depression (Schecklmann et al., 2014). Thus, the impact of the tinnitus might be experienced as more impairing and covering more areas in daily life and mental health. This may also be one reason why in direct comparison to participants with similar hearing loss, the chronic tinnitus sensation seems to be associated with more alterations in the brain (for instance association of cognitive abilities and resting state coupling which was seen in tinnitus patients but not in control participants of similar hearing loss). However, research on this topic is to date entirely missing but may give valuable insights into mental health problem associated with age-related hearing loss and chronic tinnitus.

3.4 Different and similar brain regions in hearing loss and tinnitus

The important brain regions in hearing loss and chronic tinnitus that have been presented in my studies show only minimal overlap. While in hearing loss frontal cortex, auditory cortex and dorsal attention network seem to be important, chronic tinnitus seem to be associated with alterations in frontal cortex, fornix, precuneus and default mode network. This might be related to different measures used in the analysis, as there have been associations with the degree of hearing loss, listening effort and audiovisual abilities in age-related hearing loss whereas in tinnitus there were relationships between brain measures and the sensation of tinnitus, tinnitus distress and cognitive abilities. Hence, it seems to make sense that different consequences of each hearing loss and tinnitus are reflected in different neural alterations. Interesting for future research may be to investigate similar consequences such as listening effort or cognitive abilities and their relation to brain structure and function in tinnitus and age-related hearing loss.

Interesting is that a group comparison in grey matter volume between normal-hearing and hard of hearing participants indicated significant grey matter volume reductions in the left middle frontal gyrus in the hard of hearing group (Rosemann & Thiel, 2020b). In contrast, the group comparison of tinnitus (with hearing loss) and control participants (with hearing loss) showed higher grey matter volume in the right middle frontal gyrus in tinnitus patients (Rosemann & Rauschecker, 2022). Hence, there seem to be some similarities in important brain regions in age-related hearing loss and chronic tinnitus although there was lower grey matter volume in hearing loss and higher grey matter volume in tinnitus. The involvement of the frontal lobe may be related using cognitive resources in order to deal with the increased listening effort or the annoyance of the tinnitus sensation. Other studies have also shown that the middle frontal gyrus plays a role in speech perception and specifically under adverse listening

conditions (Giroud et al., 2018; Rudner et al., 2019; Wong et al., 2010). Further, research demonstrated the role of the middle frontal gyrus in tinnitus distress as a kind of control mechanism to decrease awareness and annoyance of the tinnitus sensation (Carpenter-Thompson et al., 2014, 2015; Golm et al., 2013; Husain, 2016). Hence, the middle frontal gyrus seems to be important in both age-related hearing loss and chronic tinnitus although the underlying function may be different.

Similarly, there was no group difference in resting-state functional connectivity (using similar seed regions such as auditory cortex and dorsal attention or default mode networks) between normal-hearing and hard of hearing participants (Rosemann & Thiel, 2019) nor between tinnitus patients and control participants with similar hearing loss (Rosemann & Rauschecker, 2023a). Hence, neither mild to moderate degrees of hearing loss nor the chronic tinnitus sensation seemed to be related to altered functional resting state coupling. In other words, neither the decrease in hearing nor the chronic perception of the tinnitus signal seems to be related to resting state coupling of the auditory cortex or several other resting state networks. Based on previous literature by other researchers (Dobel et al., 2023; Hullfish et al., 2019; Husain, 2016; Leaver et al., 2016; Schmidt et al., 2017), changes in resting state functional connectivity seem to be important in the chronification of the tinnitus sensation, however this cannot be assessed in cross-sectional studies as the presented ones. Unfortunately, there is currently only limited knowledge on the chronification mechanisms of tinnitus based on longitudinal studies. Similarly, longitudinal studies with several stages of hearing loss may show differences in resting state coupling as other studies including mild to severe stages of hearing loss indicated associations with resting state functional connectivity of the salience and dorsal attention networks (Chen et al., 2018; Husain et al., 2014; Schmidt et al., 2013; Schulte et al., 2020). Hence, changes in resting state coupling may arise due to severe declines in hearing and during the chronification process of the tinnitus signal. However, these two assumptions need to be clarified by future longitudinal research.

3.5 Summary

To sum up, the presented work demonstrated that age-related hearing loss and tinnitus are related to different structural and functional changes in the brain. We hereby provided novel insights into neural mechanisms of hearing loss and tinnitus that are crucial for advancing treatment options as well as evaluating the efficacy of hearing loss and tinnitus interventions. There seem to be more profound neural changes associated with chronic tinnitus than with age-related hearing loss and different brain regions seem to be important. However, a closer look at all those studies also showed similarities: such that the middle frontal gyrus seems to be play an important role in tinnitus and hearing loss as well although the underlying mechanism may be different. Further, changes in resting state functional connectivity seem to be not associated with the hearing loss or chronic perception of tinnitus per se,

but are related to the consequences of those – such as increased listening effort, changes in audiovisual integration and cognitive abilities.

As mentioned earlier, it is crucial to differentiate between hearing loss and tinnitus in order to draw meaningful conclusions: studies on age-related hearing loss should exclude participants with tinnitus while studies on chronic tinnitus should be carefully controlled for hearing loss. However, future research may add valuable knowledge on similarities and differences of neural changes in age-related hearing loss and chronic tinnitus by including three groups of participants (normal-hearing, hard of hearing without tinnitus and hard of hearing with chronic tinnitus). This study design may aid in disentangling structural and functional alterations that arise due to the hearing loss and due to the tinnitus perception. Further, one should also consider assessing similar outcome measures in those populations. While behavioral outcomes in hearing loss are mostly focused on speech perception, audiovisual abilities and listening effort, research in tinnitus mostly covers mental health problems like sleep problems, depression and anxiety. Hence, assessing similar consequences on both abilities relating to perceptual problems but also those relating to mental health may add valuable knowledge on everyday life consequences of hearing loss and tinnitus. Insights on how these are reflected in neural changes would further lead to significant advancements in the field specifically regarding finding suitable treatment options.

4. Publication list

*Publications submitted with the habilitation thesis are marked with a **

- **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 (Impact Factor: 1,9)
- **Rosemann, S.**, Brunner, F., Kastrup, A., Fahle, M. (2017). Musical, visual and cognitive deficits after middle cerebral artery infarction, eNeurologicalSci, Volume 6, 25 – 32. doi:10.1016/j.ensci.2016.11.006 (Impact Factor: 0,571)
- **Rosemann, S.**, Wefel, I., Elis, V., Fahle, M. (2017). Audio-visual interaction in visual motion detection: Synchrony versus Asynchrony, Journal of Optometry, 10(4), 242–251. doi:10.1016/j.optom.2016.12.003. (Impact Factor: 0,653)
- **Rosemann, S.**, Gießing, C., Özyurt, J., Carroll, R., Puschmann, S., Thiel, C. M. (2017). The contribution of cognitive factors to individual differences in understanding noise-vocoded speech in young and older adults, Frontiers in Human Neuroscience, 11:294. doi: 10.3389/fnhum.2017.00294 (Impact Factor: 3,473)
- ***Rosemann, S.** & Thiel, C. M. (2018). Audio-visual speech processing in age-related hearing loss: stronger integration and increased frontal lobe recruitment, NeuroImage, 175, 425-437, https://doi.org/10.1016/j.neuroimage.2018.04.023 (Impact Factor: 7,4)
- ***Rosemann, S.** & Thiel, C. M. (2019). The effect of age-related hearing loss and listening effort on resting state connectivity. Scientific Reports, 9:2337. doi: 10.1038/s41598-019-38816-z (Impact Factor: 4,6)
- Puschmann S., Daeglau M., Stropahl M., Mirkovic B., **Rosemann S.**, Thiel C. M., Debener S. (2019). Hearing-impaired listeners show increased audiovisual benefit when listening to speech in noise. NeuroImage, 196, 261-268, https://doi.org/10.1016/j.neuroimage.2019.04.017 (Impact Factor: 7,4)
- ***Rosemann, S.** & Thiel, C. M. (2020). Neural signatures of working memory in age-related hearing loss. Neuroscience, 429, 134-142, https://doi.org/10.1016/j.neuroscience.2019.12.046 (Impact Factor: 3,7)
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- Vogelzang, M., Thiel, C. M., **Rosemann, S.**, Rieger, J. M. & Ruigendijk, E. (2020). Neural mechanisms underlying the processing of complex sentences: an fMRI study. Neurobiology of Language, 1(2), 226–248. https://doi.org/10.1162/nol_a_00011 (Impact Factor: 3,63)
- ***Rosemann, S.** & Thiel, C. M. (2020). Neuroanatomical changes associated with age-related hearing loss and listening effort. Brain Structure and Function, 225(9), 2689-2700. https://doi.org/10.1007/s00429-020-02148-w (Impact Factor: 3,748)
- *Schulte, A., Thiel, C. M., Gieseler, A., Tahden, M., Colonius, H. & **Rosemann, S.**, (2020). Reduced Resting State Functional Connectivity with Increasing Age-Related Hearing Loss and McGurk

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- Vogelzang, M., Thiel, C. M., **Rosemann, S.**, Rieger, J. M. & Ruigendijk, E. (2021). Effects of age-related hearing loss and hearing aid experience on sentence processing. Scientific Reports, 11:5994. https://doi.org/10.1038/s41598-021-85349-5 (Impact Factor: 4,6)
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- ***Rosemann, S.**, Gieseler, A., Tahden, M., Colonius, H. & Thiel, C. M. (2021). Treatment of age-related hearing loss alters audiovisual integration and resting-state functional connectivity: A randomized controlled pilot trial, ENeuro. https://doi.org/10.1523/ENEURO.0258-21.2021 (Impact Factor: 4,363)
- ***Rosemann, S**., & Rauschecker, J. P. (2022). Neuroanatomical alterations in middle frontal gyrus and the precuneus related to tinnitus and tinnitus distress. Hearing Research, 108595. https://doi.org/10.1016/j.heares.2022.108595 (Impact Factor: 3,67)
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- ***Rosemann, S**., & Rauschecker, J. P. (2023). Increased fiber density of the fornix in patients with chronic tinnitus revealed by diffusion-weighted MRI. Front. Neurosci. 17:1293133. https://doi.org/10.3389/fnins.2023.1293133 (Impact Factor: 3,5)

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Erklärungen

Darlegung der Anteile aller Autoren an den wissenschaftlichen Einzelarbeiten der kumulativen Habilitationsschrift

I was involved in the substantial contributions to the conception or design of the work in all articles that are part of the cumulative habilitation thesis. Most manuscripts were written by me as a first author or supervised by me. I outline the contributions of my coauthors for all listed articles below:

- **Rosemann, S. & Thiel, C. M. (2018, 2019, 2020a, 2020b, 2021)**
  - Substantial contributions to the conception or design of the work: SR, CMT
  - Acquisition of the data: SR (except 2020a which was done by student assistants)
  - Analysis of the data: SR
  - Interpretation of the data: SR, CMT
  - Drafting the work: SR
  - Revising the work critically: CMT
  - Final approval of the version to be published: SR, CMT
  - Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved: SR, CMT

- **Rosemann, S., Smith, D., Dewenter, M. & Thiel, C. M. (2020)**
  - Substantial contributions to the conception or design of the work: SR, CMT
  - Acquisition of the data: DS, MD
  - Analysis of the data: SR, DS, MD
  - Interpretation of the data: SR, CMT
  - Drafting the work: SR
  - Revising the work critically: CMT
  - Final approval of the version to be published: all authors
  - Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved: SR, CMT

- **Schulte, A., Thiel, C. M., Gieseler, A., Tahden, M., Colonius, H. & Rosemann, S., (2020)**
  - Substantial contributions to the conception or design of the work: SR, CMT, AG, MT, HC
  - Acquisition of the data: AG, MT
  - Analysis of the data: AS
  - Interpretation of the data: AS, SR, CMT
  - Drafting the work: AS
  - Revising the work critically: SR
  - Final approval of the version to be published: all authors
  - Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. SR

- **Pauquet, J., Thiel, C. M., Mathys, C. & Rosemann, S. (2021)**
  - ❖ Substantial contributions to the conception or design of the work: SR, JP, CMT
  - ❖ Acquisition of the data: JP
  - ❖ Analysis of the data: JP, CM
  - ❖ Interpretation of the data: JP, SR, CMT
  - ❖ Drafting the work: JP
  - ❖ Revising the work critically: SR
  - ❖ Final approval of the version to be published: all authors
  - ❖ Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved: SR

- **Rosemann, S., Gieseler, A., Tahden, M., Colonius, H. & Thiel, C. M. (2021)**
  - Substantial contributions to the conception or design of the work: SR, CMT, AG, MT, HC
  - Acquisition of the data: AG, MT
  - Analysis of the data: SR, AG
  - Interpretation of the data: SR, CMT, AG
  - Drafting the work: SR, AG
  - Revising the work critically: CMT, HC
  - Final approval of the version to be published: all authors
  - Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. SR, CMT

- **Rosemann, S., & Rauschecker, J. P. (2022, 2023a, 2023b)**
  - ❖ Substantial contributions to the conception or design of the work: SR, JPR
  - ❖ Acquisition of the data. SR
  - ❖ Analysis of the data: SR
  - ❖ Interpretation of the data: SR, JPR
  - ❖ Drafting the work: SR
  - ❖ Revising the work critically: JPR
  - ❖ Final approval of the version to be published: all authors
  - ❖ Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved: SR, JPR

Erklärung zur selbstständigen Verfassung der Arbeit und der verwendeten Hilfsmittel

Hiermit versichere ich, dass ich die vorliegende Habilitationsschrift selbstständig verfasst und nur die angegebenen Quellen verwendet und die „Ordnung über die Grundsätze zur Sicherung guter wissenschaftlicher Praxis an der Carl von Ossietzky Universität“ beachtet habe.

Erklärung über frühere Antrage auf Zulassung zur Habilitation

Hiermit versichere ich, dass die vorliegende Arbeit weder in ihrer Gesamtheit noch in Teilen einer anderen wissenschaftlichen Hochschule zur Begutachtung in einem Habilitationsverfahren vorliegt oder vorgelegen hat.

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Stephanie Rosemann