General Discussion
The studies described in this thesis aimed to 1) systematically review the existing literature on the possible connections between hearing impairment and parasympathetic nervous system activity (Chapter 2), 2) provide a theoretical framework and methodological knowledge to support the future implications using pupil light reflex as a test method to investigate the association between hearing impairment and parasympathetic nervous system activity (Chapter 2 and 3), 3) investigate the relationships between hearing acuity, daily-life fatigue and task-evoked pupil dilation during speech comprehension in noise task (Chapter 4), and 4) unravel the possible role of the parasympathetic nervous system activity in the pupil dilation response during speech comprehension in noise tasks (Chapter 5). In the current Chapter (6), the main findings of the thesis are presented first, followed by a description of the methodological considerations, recommendations for future research and implications for clinical practice. Finally, this chapter includes a short summary highlighting the most important conclusions.

6.1 MAIN FINDINGS

Lack of studies investigating the relationships between hearing impairment and parasympathetic nervous system

In Chapter 2 the possible relationships between the parasympathetic nervous system (PNS) and hearing impairment (HI) were examined by systematically reviewing the existing literature. Till the date that the search was finished (30th October 2014), only two relevant studies addressing the association between hearing impairment and PNS activity were identified (Hasson et al. 2009; Mackersie et al. 2015). Hasson et al. (2009) measured the heart rate variability (HRV) of orchestra musicians with different degrees of hearing problems. They found that the high-frequency (HF) component of the HRV, an indicator of the cardiovascular PNS activity, was negatively correlated with hearing problems. The other study also measured the HRV in participants with normal hearing (NH) and HI during the sentence recognition in noise task (Mackersie et al. 2015). The results indicate that the HF component of the HRV was lower in participants with hearing loss than in normally-hearing participants at the lower (more difficult) signal to noise ratios. Thus, both studies found a reduced PNS activity in participants with worse hearing ability, as shown by the HF component of HRV. The fact that only two studies were identified in this research area indicates a huge gap in knowledge in this topic area. Overall, it can be concluded there is too little evidence to draw any concrete conclusions about the associations between hearing impairment and PNS activity. As a result, Chapter 2 pointed out the need for future studies to further investigate the relationships between HI and PNS. Fortunately, more studies started to bridge this knowledge gap shortly after the systematic review came out (Francis et al. 2016; Mackersie & Calderon-Moultrie 2016). The studies presented in Chapters 4 and 5 further dig into
Pupil light reflex as an effective measure for parasympathetic nervous system activity

Chapter 2 and 3 focused on the theoretical and methodological aspects of using the pupil light reflex (PLR) to evaluate PNS activity. The systematic review presented in Chapter 2 investigated the relationships between PLR and PNS activity by reviewing the sensitivity of PLR as a testing method to differences between patients with PNS-related dysfunctions (e.g. Parkinson’s diseases, Alzheimer’s disease, diabetes) and healthy controls. Most of the existing literature found at least one PLR parameter (e.g. maximum constriction velocity, constriction amplitude) to be significant between the patient group and control group.

Based on the theoretical ground provided by the review, in Chapter 3, we developed a PLR measurement tool using a computer screen to generate the light stimuli and compared this method with the more commonly system using light-emitting diode (LED) to evoke the light stimuli. The test-retest reliability of both set-ups was examined and we demonstrated that the computer screen set-up allows a sensitive and reliable registration of the PLR, whose reliability is similar to that of the PLR generated by a LED set-up. In addition, associations between PLR parameters and Need for Recovery (NfR), which was assumed to be associated with PNS related activity, was observed as well. Higher levels of need for recovery were associated with higher levels of PNS activity as reflected by PNS related PLR parameter values in healthy individuals.

The relationships between hearing acuity, daily-life fatigue and pupil dilation during speech comprehension in noise task

Chapter 4 described the study to investigate the relationships between hearing acuity, daily-life fatigue and task-induced pupil dilation response during the speech comprehension in noise task. In Chapter 4, listening effort during the speech reception threshold (SRT) test targeting 50% correct response was objectively indexed by peak pupil dilation (PPD) for both NH and HI participants. Self-reported daily-life fatigue was measured by the NfR and the Checklist Individual Strength (CIS) questionnaires. Hearing acuity was determined by pure-tone average (PTA) and Speech Intelligibility Index (SII). The results indicate that both daily-life fatigue and hearing acuity showed significant, and almost equal, negative associations with the PPD during listening. Less fatigue and better auditory sensitivity were associated with larger PPDs during the SRT test. However, the detailed interactions between listening effort, fatigue and hearing loss remain unclear. Chapter 5 includes an attempt to further explain these interactions by including PNS activity in the analyses, and the findings will be discussed in the paragraph below.
The role of PNS during effortful listening

One of the main motivations to initiate the research described in this thesis is to answer the question of why HI participants showed smaller PPD during the challenging (e.g. 50% intelligibility level) speech recognition in noise task than their NH peers, and the answer might lie in the contribution of parasympathetic activity. When recording the pupil size in dark, the PNS has minimum influence on the task-evoked pupil dilation in response to cognitive processing. In contrast, in light, the pupil dilation in response to increased resource allocation is partly mediated by the inhibitory effect via the parasympathetic pathways (Steinhauer et al. 2004). Therefore, comparing the pupil dilation response during speech comprehension tasks in dark and light conditions enables a closer examination of the relationship between HI and PNS activity.

The study presented in Chapter 4 covers an experiment in which the pupil dilation response was recorded during the SRT test in the presence of ambient light. In Chapter 5, a dataset supplementing that of Chapter 4 by providing pupil dilation data recorded in the same participants in darkness. The results showed no difference in the PPD between NH and HI groups in darkness, while the PPD was significantly larger for NH participants than listeners with HI in the light condition. This result might indicate that the contribution of SNS activation to the pupil dilation response is similar between the two groups of listeners. The larger PPD observed for NH participants when testing in a light condition might indicate a smaller inhibitory effect via the PNS pathway (i.e. more PNS activation) on the PPD for the HI group than for the NH group during the test.

In addition, the study described in Chapter 5 found an interaction effect of NfR groups (defined by median NfR score, high-NfR vs low-NfR) and hearing status (NH vs HI) on the difference between PPD in dark and light. Only NH participants with low-level NfR showed a larger PPD in light than in dark condition, which indicates larger inhibition via the PNS pathway of the PPD during listening (i.e. less PNS activation). These data confirm the findings in Chapter 3 showing that lower-level NfR was associated with a smaller PLR, a sign of a less activated PNS. The difference in PPD between dark and light was much smaller in participants with HI and/or participants with a relatively high-level of NfR, thereby suggesting that HI listeners and/or listeners with a high-level of NfR are more likely to have a more activated PNS.

Given the role of PNS in control of the ‘rest and digest’ activity, the findings observed in Chapter 5 may suggest that some sort of a coping mechanism of the PNS becomes active to adapt to the presence of a high level of need for recovery and/or hearing impairment. The PNS acting like ‘man with the hammer’, a commonly used term among cycling folklore to describe the adverse effect during sustained cycling, during sustained cognitive processing including effortful listening. Apparently, the PNS becomes more activated in order to increase the restoration ability of the human body to cope with the higher need for recovery and hearing loss. As a consequence,
other functions of the body including the cognitive resources allocation and pupil dilation response could be suppressed. Thus, reduced pupil dilation during effortful listening could be a by-product of the ‘man with the hammer’ effect from the PNS. In all, this finding of the role of the PNS during effortful listening as the ‘man of the hammer’ is the most novel and important finding of the current thesis. This finding emphasizes the importance of PNS in coping with hearing problem and higher need for recovery, and again, points out the needs for future studies to gain more insights into the relationship between PNS and hearing impairment.

6.2 METHODOLOGICAL CONSIDERATION

Pupil light reflex

Pupil light reflex (PLR) as a method to evaluate PNS activity has its strengths and limitations. Comparing to other PNS measurements, PLR provides a non-intrusive, fast and relatively easy (that you can even measure it with a computer screen as suggested in Chapter 3) way to measure the PNS activity. Meanwhile, as pointed out in Chapter 2, PLR has been found to be a sensitive method to evaluate a variety of PNS dysfunctions. However, PLR also has some methodological considerations which will be discussed in more details below.

Sensitive to the characteristics of the light stimuli

The PLR is a reflex in response to light. Therefore, this method is highly sensitive to the characteristics of the light stimuli, including color (Fan et al. 2009a; Ishikawa et al. 2012), light intensity (Bakes et al. 1990; Bitsios et al. 1999a; Fan et al. 2009b), and duration (Pong & Fuchs 2000) of the light. In Chapter 2, the systematic review study pointed out a lack of standardization in the assessment of PNS activity using PLR measurements. This is mainly due to the various types of light stimuli that have been used in different studies which makes it almost impossible to compare the absolute PLR values across studies. The pilot study described at the end of Chapter 3 reports how the PLR as measured with a computer screen set-up responds to light stimuli characterized by different colors, light intensities and durations. This insight may contribute to the further standardization of a valuable method to evaluate PNS activity.

Sensitive to other factors including cognitive processing

Other than the characteristics of the light stimuli, the PLR is also sensitive to many external factors. To illustrate, the PLR has been found to be sensitive to aging (Bitsios et al. 1996a), gender (Fan et al. 2009c), sleepiness (McDougal & Gamlin 2015) and smoking (Morte et al. 2005). In addition, although the PLR is commonly considered as a low-level reflex that occurs without the modulation of higher-level processing. However, there is mounting evidence showing that the PLR could be
influenced by cognitive processing as well. Steinhauer et al. (2000) investigated the PLR during mental arithmetic tasks, and they found reduced PLR constriction in conditions requiring high levels of mental effort. Another interesting study by Naber & Nakayama (2013) showed that viewing pictures with a sun induced larger pupil constriction than pictures without a sun, even though all pictures had the same level of light intensity. This result might suggest that PLR can be modulated by higher-level visual processing. In addition, multiple studies reported covertly attending to a brighter region of the visual field is sufficient to drive a pupillary constriction (Binda et al. 2013a; Mathôt et al. 2013). A recent study suggested that the attentional modulation of the PLR is related to the activity of frontal eye fields, a prefrontal cortical area governing the movements and attention of the eye (Binda & Gamlin 2017; Ebitz & Moore 2017). For those who wish to measure PLR in their future studies, extra caution is needed as one needs to control for these external factors (e.g. find an age-matched control group if want to perform group comparison on the PLR parameters).

**PLR parameters**

   Multiple parameters can be extracted from a simple PLR trace. Chapter 2 listed the relevant parameters found in the literature, including:
   • maximum constriction velocity (MCV), (the maximum slope of the constriction)
   • maximum constriction acceleration (MCA), (the maximum value of the second derivative of constriction)
   • absolute constriction amplitude (ACA), (the amplitude difference between baseline and minimum pupil diameter of the constriction)
   • relative constriction amplitude (RCA), (the ratio of ACA to baseline pupil diameter (BPD), expressed as a percentage)
   • latency, (the time between light stimulus onset and constriction onset);
   • constriction time, (the time from the end of latency period to the moment of maximum constriction)

After reviewing the sensitivity of these parameters to detect PNS dysfunction, we suggest that the MCV and RCA are the PLR parameters that are most likely sensitive to PNS dysfunction. Conversely, in Chapter 3, RCA was found to be related to SNS activity, indicating that RCA is not a pure PNS-indicator. Therefore, it is not fully clear yet whether all known PLR parameters purely reflect PNS activity or a combination of both PNS and SNS activities. More studies need to be done to disassociate the PNS and SNS contributions in the PLR parameters.

**Task-evoked pupil dilation response**

*Influence of need for recovery and fatigue (long-term daily life fatigue and task-induced fatigue)*
Task-evoked pupil dilation response during the speech comprehension in noise task has been considered as a measurement of listening effort. The studies presented in Chapters 4 and 5 showed that daily-life fatigue and need for recovery can also influence the PPD of the pupil dilation response. It should be noted that the fatigue and need for recovery in Chapter 4 and 5 were measured subjectively via the self-reported questionnaires (CIS and NfR), and were corresponding to long-term fatigue in daily-life situations.

Task-induced fatigue, the fatigue caused by sustained mental effort may also alter the pupil dilation response. For example, Hopstaken and colleagues (2015a, b) conducted visual N-back tasks for 2 hours while recording the pupillary response at the same time. In Hopstaken et al. (2015b), the result showed that the mean task-evoked pupil dilation across time was strongly correlated to subjective ratings of fatigue, such that a smaller mean pupil dilation was found to co-occur with evidence of increasing time-on-task fatigue. Similarly, Zekveld et al. (2010) found decreasing baseline pupil diameters and decreasing PPD as time on task increased. The baseline pupil diameter, which is closely related to task engagement and arousal under the control of the locus coeruleus norepinephrine (LC-NE) system (Beatty 1982; Aston-Jones & Cohen 2005), was also found to be associated with time-on-task fatigue by Hopstaken et al. (2015a). Therefore, it is suggested that the influence of task-induced fatigue to the pupil dilation response may be driven by the LC-NE system.

The above findings address the influence of fatigue (both long-term and task-induced fatigue) to the pupil dilation response. Therefore, it is important for any future researchers to take the influence of fatigue and need for recovery into consideration when designing their future pupillometry experiments.

### 6.3 RECOMMENDATIONS FOR FUTURE RESEARCH

#### Combine pupillometry with other autonomic measurements

This thesis presents studies measuring pupil responses, both dilation and constriction and the contribution of PNS in these responses. It remains unclear however whether the PNS activity measured by pupillometry is consistent with the activity evaluated by other measurements like heart rate variability (HRV) and skin conductance.

Chapter 2 identified a few studies that measured PLR and HRV at the same time (Pfeifer et al. 1985; Perry et al. 1989; Levy et al. 1992; Bar et al. 2008). Although most of the studies found that the PLR results were in line with the findings from cardiovascular measurements, it would be premature to conclude the consistency between the two measures on the basis of so relatively little evidence. In addition, there is some evidence suggesting that HRV indicators are not assessing exactly the same dimension of PNS activity as the pupil parameters do (Bär et al. 2009; Daluwatte et al. 2012). As a result, future research is needed to systematically examine the consis-
tency between PLR and other PNS measurements.

Similarly, the consistency between listening effort measured by task-evoked pupil dilation response and other autonomic measurements during the speech comprehension tasks in noise task also remains unclear. Regardless of the fact that there are more studies which started to examine listening effort during auditory tasks by measuring ANS activity (Mackersie et al. 2015; Francis et al. 2016; Mackersie & Calderon-Moultrie 2016), there is only one study available that compared the results obtained through pupillometry with the ANS activity indexed by cortisol levels (Kramer et al. 2016). Further work involving pupillometry and other ANS-related measurements during speech comprehension in noise task is needed to be able to better examine the relative sensitivity of these measures.

Last but not least, since pupillometry is a non-intrusive measure, it can be easily measured simultaneously with other commonly used measurements in cognitive hearing science (e.g. EEG and fMRI). Therefore, I recommend future research to consider using pupillometry as a supplementary measurement if possible.

**Unravelling the input of PNS and SNS to the dynamic pupil response**

The pupil response is under the direct control of the PNS and SNS of the ANS. Still, little is known about the exact contributions of these two systems to the pupil response.

For PLR, effort has been made to quantify the PNS and SNS inputs by constructing mathematic models. Usui & Hirata (1995) and Yamaji et al. (2000) proposed a modeling method called ‘pupillary muscle plant’, where tension of the sphincter and dilator muscle, as well as the SNS and PNS contribution were considered as the input of the model system. By inverse dynamic modeling, they were able to estimate the PNS contribution based on PLR response, and the whole model was validated by experimental testing. Fan & Yao (2011) built a similar model where PNS activity was considered as part of the input. They extracted the PNS contribution from experimental data and found a higher PNS activity in females than in males. However, as pointed out in Methodological Considerations earlier in this chapter, PLR is really sensitive to the characteristics of the light stimuli and other external factors, making it more complex for modelling. Further research may be needed in order to provide a model taking these factors as inputs.

As for the task-induced pupil dilation response during cognitive processing, Steinhauer & Hakerem (1992) proposed a hypothesized model covering the relative contribution of PNS and SNS activations to the pupil dilation during the cognitive task. **Figure 6-1** is from the original works of Steinhauer and Hakerem (1992) which depicts their model. First, there is an early dilation component mainly driven by the inhibitory effect to the pupil dilation via the PNS pathways. This effect is minimum in darkness and becomes more apparent when the ambient light intensity increased. Later, the SNS component kicks in via the direct SNS simulation of the pupillary dilator muscle to further dilate the pupil regardless of the presence of ambient light.
However, the proposed model is only on a theoretical basis. With the help of new pupillometry analysis approaches like growth curve analysis, future studies may be able to refine the model and put it into practice.

**Measuring the pupil response in real-life scenarios**

The experimental studies presented in the current thesis were all conducted in a laboratory environment. Even though laboratory studies are able to provide strict control of the test stimuli (auditory and visual) and the test environment (ambient light and acoustic condition), there is still a need to measure the pupil response in real-life scenarios. This is particularly important for task-induced pupil dilation during effortful listening, as the communication in social context is usually more complex and effortful (e.g. cocktail party environment). With the growing availability of remote eyetracker (e.g. wearable glasses mounting with infrared cameras), it becomes possible to record pupil dilation in realistic situation. However, the biggest challenge for a real-life pupil dilation measure is how to eliminate the influence of light reflex, as the light intensity varies dramatically in daily-life situations (Teich & Saleh 1991). Nevertheless, virtual reality (VR) devices are able to provide immersive experience while recording pupil response at the same time. Simulating realistic communication tasks via a VR device can be a temporary solution to measure pupil dilation in a
semi-realistic scenario.

**Need for Recovery scale and its usage in future pupillometry studies**

In the experimental studies presented in Chapter 3 to 5 of the current thesis, the NfR scale has been used as a subjective measurement to assess the need for recovery after work for participants with both normally hearing and hearing impairment. This short 11-item has been found to be positively correlated to the constriction of PLR (Chapter 3), and negatively correlated to PPD during the SRT task targeting 50% correct response that measured in light (Chapter 4 and 5). Larger PLR constriction and smaller PPD during cognitive processing can both be seen as signs for higher-level of PNS activity. And due to the ‘rest and digest’ role of PNS, it is expected NfR is positively related to PNS activity. Therefore, the correlations between NfR and pupil dynamics fulfilled the initial expectations. For any future research measuring pupil response, this short scale can be facilitated as a supplementary measure to provide extra information about need for recovery, daily-life fatigue and PNS activity.

**6.4 IMPLICATIONS FOR CLINICAL PRACTICE**

**Pupil light reflex as a clinical measure of PNS activity**

There is growing interest in the psychophysiological impact of hearing impairment within the field of audiology. PNS activity, as discussed in previous chapters of this thesis, plays an important role in response to both hearing impairment and higher-level NfR. Thus, a reliable measure of PNS activity would be of considerable value for audiological practice. However, there are only few studies available examining the associations between hearing impairment and PNS activity, and apparently no ‘ready-for-clinic’ test to evaluate the PNS activity in hearing-impaired listeners in existence yet.

One of the main focuses of the current thesis is to provide the theoretical and methodological background knowledge needed for the future use of PLR as a measure of the PNS activity. In Chapter 2, a systematic review suggests that PLR has been extensively measured as an effective clinical tool to examine PNS dysfunction. This is the theoretical foundation to use the PLR to seek the presence of possible PNS dysfunction within hearing-impaired listeners. A practical solution using computer screen to generate the light stimuli for the PLR has been given in Chapter 3, which provides the methodology support for PLR’s future usage in clinical audiology. Measuring the PLR of normally-hearing and age-matched hearing-impaired listeners in a lab setting could be an important first step.
6.5 CONCLUSION

This thesis had two main goals. The first goal was to provide the theoretical framework and methodology to support the future implications using pupil light reflex as a testing tool to investigate the association between hearing impairment and parasympathetic nervous system activity. The second goal was to unravel the possible role of parasympathetic nervous system during to the pupil dilation response during speech comprehension in noise tasks. Based on the results described in this thesis, it is concluded that:

- There is a big gap in knowledge on the exact role of the relative contributions of the SNS and PNS in hearing (impairment) and the pupil response
- Higher levels of need for recovery (or fatigue) are associated with faster and larger pupil constriction of pupil light reflex, suggesting increased levels of parasympathetic nervous system activity in people experiencing higher daily levels of need for recovery.
- Daily-life fatigue and hearing acuity independently and equally contribute to the pupil dilation response; people with higher levels of daily-life fatigue and worse hearing acuity show smaller pupil dilation during speech perception targeting 50% correct performance.
- Elevated levels of parasympathetic nervous system activity in people with hearing loss and/or fatigue during challenging listening conditions may indicate that the parasympathetic system helps to restore energy and prevent an overload of stress.

This thesis provides new insights into the psychophysiological impact associated with hearing impairment, and presents a possible tool and knowledge for future work aimed at further evaluation of this impact.