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RESPIRATORY INFLUENCES ON PUPIL SIZE DYNAMICS AND VISUAL RECOGNITION MEMORY

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Respiratory influences on pupil size dynamics and visual recognition memory

Thesis for Doctoral Degree (Ph.D.)

By

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Für meine Eltern, die mir alles ermöglicht haben.

Populärwissenschaftliche Zusammenfassung der Dissertation

Sekunden nach der Geburt machen wir unseren ersten Atemzug. Der Übergang von einem Leben mit flüssigkeitsgefüllten Lungen, das auf die Zufuhr von Sauerstoff durch die Nabelschnur angewiesen ist, zu einer autonomen Atmung erfolgt fast augenblicklich. Von diesem Moment an ermöglicht die Atmung unser Leben, meist unbewusst. Aktuelle Forschung zeigt darüber hinaus, dass die Atmung eine komplexe Rolle hat, die weit über die physiologischen Vorgänge hinausgeht. Es hat sich gezeigt, dass die Atmung spezifische Aktivitätsmuster im gesamten Gehirn auslöst, die ihrerseits verschiedenen Wahrnehmungs- und kognitiven Prozessen zugrunde liegen. Vermutet wird, dass die Atmung diese Prozesse direkt beeinflusst.

Seit langem wird angenommen, dass sich die Pupillen beim Einatmen weiten und beim Ausatmen verengen. Neure Studien zeigen darüber hinaus, dass die Atmung die visuelle Gedächtnisleistung und die Wahrnehmungsschwellen beeinflussen kann, wobei insbesondere die nasale Einatmung begünstigt wird. Diese Studien weisen jedoch eine Reihe von methodologischen Problemen auf, die ihre Validität in Frage stellen.

Einige dieser methodologischen Schwächen sollen in der vorliegenden Arbeit überwunden werden. Zunächst wurde eine systematische Literaturrecherche über den Zusammenhang zwischen Atmung und Pupillengröße durchgeführt, um die weit verbreitete Annahme zu untersuchen, es gäbe qualitativ hochwertige Belege dafür, die Atmung beeinflusse die Pupillengröße. Hieran schloß sich eine experimentelle Studie an, die eine subtile, aber systematische Veränderung der Pupillengröße während des Atemzyklus zeigte. Die erhobenen Daten deuten entgegen der landläufigen Meinung darauf hin, die Pupillengröße nehme beim Ausatmen stärker zu als beim Einatmen. Ebenso wurde eine falsche Korrelation zwischen Atmung und Pupillensignalen, die von der Atemfrequenz beeinflusst wird, beobachtet, die Ergebnisse früherer Studien verzerrt haben könnte und die in Folgestudien berücksichtigt werden sollte.

In einem nächsten Schritt wurde überprüft, ob die Atmung die visuelle Gedächtnisleistung beeinflusst, wie bisher angenommen. In zwei unabhängigen Studien fand ich keinen Hinweis für einen signifikanten Einfluss der Atmungsrate oder des Atemwegs auf die visuelle Gedächtnisleistung. Dieses Ergebnis unterstreicht die Notwendigkeit stringenterer Methoden, um die widersprüchlichen Ergebnisse in diesem Forschungsbereich miteinander in Einklang zu bringen.

Schließlich habe ich einen Abstecher in die Welt der chemosensorischen Wahrnehmung und ihrer Beziehung zu hormonellen oralen Kontrazeptiva gemacht. Ich habe gezeigt, dass hormonelle Kontrazeptiva entgegen früheren Annahmen weder die Geruchs- und

Geschmackswahrnehmung noch die trigeminale Wahrnehmung beeinträchtigen. Dies sollte all jene beruhigen, die orale Kontrazeptiva einnehmen oder dies in Erwägung ziehen.

Insgesamt hinterfragt diese Arbeit gängige Mythen und eröffnet ein komplexeres und differenzierteres Verständnis, wie unser Körper auf Atmung und orale Kontrazeptiva reagiert. Sollte diese Zusammenfassung Ihr Interesse geweckt haben, atmen Sie tief durch, lesen Sie weiter und lassen Sie sich von mir durch die faszinierende Welt der Atmung führen, die unser Leben beeinflussen kann - oder auch nicht.

Popular science summary of the thesis

Within seconds of birth, we take our very first breath. We transition from a life with fluid-filled lungs, dependent on umbilical cord oxygen supply, to autonomous breathing, almost instantaneously. Breathing sustains our lives from this point onwards, mostly operating non-consciously. Recent research, however, has unveiled a more intricate role for breathing, that is not limited to our physiological processes. It has been shown that breathing causes specific patterns of brain activity throughout the brain, activity that also underlies various perceptual and cognitive processes. Thus, it has been proposed that breathing directly affects these processes.

There has been a longstanding notion that inhalation causes pupil dilation while exhalation results in constriction. Moreover, recent studies have shown that breathing can affect visual memory performance and perceptual thresholds, particularly favoring nasal inhalation. However, these studies suffer from methodological issues, casting doubt on their validity.

This thesis aims to address several of these limitations. First, I conducted a systematic literature review on the connection between breathing and pupil size, challenging the prevalent belief that there is good evidence that breathing affects pupil size. Subsequently, I conducted an experimental study, revealing a subtle but systematic change in pupil size during the breathing cycle. Contrary to popular belief, the data suggests that pupil size increases during exhalation rather than inhalation. Furthermore, I identify a spurious correlation between breathing and pupil signals, influenced by breathing rate, which might have confounded previous research and should be considered in future studies.

Next, I investigated whether breathing influences visual memory performance as previously believed. In two separate studies, I found no evidence that breathing phase or route significantly impact visual memory performance. This result highlights the need for more rigorous methods to reconcile the contradictory findings in this research area.

Finally, I took a detour into the world of chemosensory perception and its relationship with hormonal oral contraceptives. I show that contrary to previous beliefs, oral hormonal contraceptives do not affect smell, taste, or trigeminal perception. This should bring reassurance to those who use or consider using oral contraceptives.

Taken together, this thesis challenges common myths and opens the door to a more complex and nuanced understanding of how our bodies respond to respiration and oral contraceptives. If this summary piques your interest, take a deep breath, keep on reading, and let me guide you through this fascinating world of how breathing may or may not shape our lives.

Abstract

Breathing, a fundamental rhythm of life, has traditionally been associated with the exchange of oxygen and carbon dioxide. However, recent research in both animal models and humans has unveiled additional roles of respiration in modulating cortical neuronal activity, influencing sensory, motor, emotional, and cognitive processes. This dissertation aims to explore the impact of respiration on pupil size dynamics and visual recognition memory in humans.

In **Study I**, we synthesized the research conducted on respiratory influences on pupil size dynamics in humans by conducting a systematic literature review. We discovered that the evidence for respiratory influences on pupil size dynamics in humans is less solid and extensive than previously believed. After more than 50 years of research, only 12 studies have directly investigated this topic. Not only was the underlying evidence for an effect of breathing phase, depth, and rate on pupil size dynamics weak, but the influence of breathing route (oral or nasal breathing) had not been investigated at all.

In **Study II**, we conducted an experimental study to answer the outstanding questions identified in **Study I**. We collected pupil size data from participants during periods of rest while they breathed through their nose and mouth, on separate occasions. We demonstrated small but significant effects of breathing phase on pupil size and a spurious correlation and phase synchronization between the breathing and the pupil signal that is largely driven by breathing rate. After accounting for this spurious correlation and phase synchronization, we show that a small but significant interaction between the breathing and the pupil signal remains. Importantly, we show that, contrary to common belief, pupil size does not increase during inhalation, but rather during exhalation. Furthermore, we did not find any changes in pupil size in the time around inhalation and exhalation, and our results were not affected by the breathing route. In conclusion, we confirmed the influence of breathing on pupil size dynamics, while uncovering a more complex and intricate relationship than previously conceived.

In **Study III**, we investigated the influence of breathing phase and breathing route on performance in a visual recognition memory task with a within-subject design and with stimuli presentation phase-locked to the inhalation or exhalation onset. We show that neither breathing phase nor breathing route affect memory performance. However, we did find an effect of breathing phase on response bias, with participants using a more conservative response bias during exhalation. Furthermore, we found that breathing route and breathing phase shape the Late Parietal Effect (LPE), but not the Frontal Negative Component (FN400), amplitude during encoding. Additionally, during recognition, both the LPE and FN400 component amplitudes were not, or only to a small extent, affected by breathing route and phase. While we demonstrated that breathing does not shape visual recognition memory performance, we also showed that breathing influences brain activity related to memory functions. Therefore, we highlight the importance of further research to elucidate the extent of respiratory influence on perception, cognition, and behavior.

In **Study IV**, we further investigated the impact of breathing on visual memory performance by investigating the effects of nasal breathing phase on memory of repeated images presented in a rapid serial visual presentation (RSVP) task. In two separate, high-powered experiments, we did not find an effect of breathing phase on task performance. An exploratory analysis in the first experiment discovered a potential performance increase for stimuli presented approximately one second after inhalation. However, this was not replicated in the second, larger, and pre-registered study. Thus, we find no effect of breathing phase on performance in this RSVP task and urge for caution regarding the notion that visual memory is broadly affected by the breathing phase.

Finally, in **Study V**, we investigated whether oral hormonal contraceptives (OC) affect chemosensory sensitivity and perception. Whereas previous research focused nearly exclusively on olfaction, we expanded this to also study the taste and trigeminal sense. Making use of Bayesian statistics, we evaluated the performance differences between a group of women taking OC, and a control group of normal cycling women. Our results indicated that the use of OC does not affect odor, trigeminal, or taste detection thresholds. Furthermore, neither odor nor taste perception were affected, with Bayes factors weighing the evidence in favor of the null hypothesis. We therefore conclude it to be unlikely that OC affect chemosensory perception to a degree that is of behavioral relevance.

Collectively, this doctoral thesis challenges prevailing myths while paving the way for a more intricate understanding of the relationship between respiration and pupil size, and perceptual and cognitive processes. Importantly, it underscores the importance of implementing rigorous methodological paradigms in future research.

List of scientific papers

I. **Schaefer**, **M**., Edwards, S., Nordén, F., Lundström, J. N., Arshamian, A. Inconclusive evidence that breathing shapes pupil dynamics in humans: a systematic review (2023). *Pflugers Arch - Eur J Physiol* **475**, 119–137. https://doi.org/10.1007/s00424-022-02729-0

II. **Schaefer**, **M**., Mathôt, S., Lundqvist, M., Lundström, J. N., Arshamian, A. Breathing-Entrained Pupil Size Dynamics: The Role of Time, Phase, Frequency, and Route (2023). *Manuscript*

III. **Schaefer**, **M**., Hrysanidis, C., Lundström, J. N., Arshamian, A. Phase-locked breathing does not affect episodic visual recognition memory, but does shape its corresponding ERPs (2023). *Manuscript under review*

IV. Thunell, E., Francis, G., Dal Bò, E., **Schaefer**, **M**., Lundström, J. N., Arshamian, A. Nasal inhalation does not improve memory of visual repetitions (2023). *Submitted manuscript*

V. **Schaefer**, **M**., Iravani, B., Arshamian, A., & Lundström, J. N. No Evidence That Hormonal Contraceptives Affect Chemosensory Perception (2021). *I-Perception*, *12*(1). https://doi.org/10.1177/2041669520983339

Scientific papers not included in the thesis

I. Hedblom, M., Gunnarsson, B., **Schaefer**, **M**., Knez, I., Thorsson, P., Lundström, J. N. Sounds of nature in the city: no evidence of bird song improving stress recovery. *Int. J. Environ. Res. Public Health*, *16*(8), 1390 (2019). https://doi.org/10.3390/ijerph16081390

II. Hedblom, M., Gunnarsson, B., Iravani, B., Knez, I., **Schaefer**, **M**., Thorsson, P., Lundström, J. N. Reduction of physiological stress by urban green space in a multisensory virtual experiment. *Sci Rep* **9,** 10113 (2019). https://doi.org/10.1038/s41598-019-46099-7

III. Seidel, M., Ehrlich, S., Breithaupt, L., Welch, E., Wiklund, C., Hübel, C., Thornton, L. M., Savva, A., Fundin, B. T., Pege, J., Billger, A., Abbaspour, A., **Schaefer**, **M**., Boehm, I., Zvrskovec, J., Rosager, E. V., Hasselbalch, K. C., Leppä, V., Sjögren, M., Nergårdh, R., Feusner, J. D., Ghaderi, A., Bulik, C. M. Study protocol of comprehensive risk evaluation for anorexia nervosa in twins (CREAT): a study of discordant monozygotic twins with anorexia nervosa. *BMC Psychiatry* **20,** 507 (2020). https://doi.org/10.1186/s12888-020-02903-7

IV. Iravani, B., Arshamian, A., **Schaefer**, **M**., Svenningsson, P., Lundström, J. N. A non-invasive olfactory bulb measure dissociates Parkinson's patients from healthy controls and discloses disease duration. *npj Parkinsons Dis.* **7,** 75 (2021). https://doi.org/10.1038/s41531-021-00220-8

V. Iravani, B., **Schaefer**, **M**., Wilson, D. A., Arshamian, A., Lundström, J. N. The human olfactory bulb processes odor valence representation and cues motor avoidance behavior. *Proceedings of the National Academy of Sciences* (2021), 118 (42). https://doi.org/10.1073/pnas.2101209118

VI. Nordén, F., Iravani, B., **Schaefer**, **M**., Winter, A. L., Lundqvist, M., Arshamian, A., Lundström, J. N. The how, when, and what of odor valence communication between the olfactory bulb and piriform cortex. *Manuscript on bioRxiv*, (2023). https://doi.org/10.1101/2023.11.02.564696

Contents

List of abbreviations

BF	Bayes factor
CCC	Copyright Clearance Center
DS	Dentate spikes
EEG	Electroencephalography
ERP	Event-related potential
EWN	Edinger-Westphal nucleus
FN400	Frontal Negative Component
GRADE	Grading of Recommendations Assessment, Development, and Evaluation
H_1	Alternative hypothesis
H_0	Null hypothesis
IML	Intermediolateral cell column
LC	Locus coeruleus
LPE	Late parietal effect
NE	Norepinephrine
OB	Olfactory bulb
OC	Oral hormonal contraceptives
OSN	Olfactory sensory neuron
preBötzC	pre-Bötzinger complex
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RRO	Respiratory-related oscillation
RSVP	Rapid serial visual presentation
SWR	Sharp wave ripples
VRM	Visual recognition memory

1 Introduction

"Then the Lord God formed a man from the dust of the ground and breathed into his nostrils the breath of life, and the man became a living being." – Genesis 2:7

Breathing[1] is fundamental to life. From the moment we are born until the moment we die, we breathe more or less non-stop, usually without thinking about it. All land-living animals use this process to breathe in oxygen and to breathe out carbon dioxide. However, during the past decade, research in animal models has shown that the role of respiration might extend much further (Cavelli et al., 2020; Heck et al., 2019; Ito et al., 2014; Tort et al., 2018; Yanovsky et al., 2014). Namely, respiration seems to modulate cortical neuronal activity and thereby influence sensory, motor, emotional, and cognitive processes (Heck et al., 2017, 2019). More recent studies are starting to indicate similar functions of respiration in humans as well, ranging from changes in visual perception across the breathing cycle (Kluger et al., 2021; Perl et al., 2019; Zelano et al., 2016), to breathing-dependent performance improvements in memory tasks (Arshamian et al., 2018; Zelano et al., 2016).

In my PhD project, I explored this emerging field by studying if and how breathing could affect perception and cognition. I have done this from the hypothesis that respiratory modulations of pupil size may mediate some of the influences of breathing on visual perception, based on past observations that inhalation is associated with pupil dilation and exhalation with pupil constriction.

Therefore, in **Studies I & II** I first set out to investigate whether various breathing parameters impact pupil size dynamics. Next, in **Studies III & IV**, I studied how breathing route and breathing phase shape episodic visual memory and its underlying neurophysiology.

Originally, I had many other research plans; however, one year into my PhD, the Covid-19 pandemic brought everything to a standstill. Homes turned into offices, and experimental research on humans became impossible. People were scared of this new disease, which typically started to manifest itself by robbing people of their sense of smell, their taste, and in the worst-case scenarios, their ability to breathe. As we tried to figure out how to stay safe, and at the same time, continue our work, we decided to abandon and postpone planned studies, and instead focus on previously collected data. This resulted in **Study V**, where we investigated potential effects of oral hormonal contraceptives on chemosensory perception. Although this study was not completely in line with the main focus of my thesis, it felt meaningful and relevant to the times.

In the first part of this thesis, I will provide a brief overview of the respiratory system, pupil function, and the interaction between breathing and behavior. Next, I will state my research aims, methods, results, and conclusions.

[1]Throughout this thesis, I will use the words "breathing" and "respiration" interchangeably.

2 Literature review

2.1 Fundamentals of breathing

2.1.1 Function & physiology

The primary function of breathing is to supply the body with oxygen and to ensure carbon dioxide release. This is a need shared by all mammals, and in general it is solved in a similar manner across mammalian species (Carvalho & Gonçalves, 2011). Body weight, lung volume, and tidal volume scale linearly in mammals, while metabolic rate scales with respiratory rate (Boggs & Tenney, 1984; Stahl, 1967).

The respiratory cycle in humans is executed 12-15 times per minute at rest, with each breath containing approximately 500 ml of air (Barrett et al., 2019b). This air is inhaled via an active process by the activation of inspiratory pump muscles that expand the ribcage using the external intercostal muscles (see Figure 2.1A), and cause the active descent of the diaphragm, thereby causing the expansion of the lungs to draw in air (Del Negro et al., 2018). Exhalation, on the other hand, is passive during breathing at rest (eupnea), and is caused by the relaxation of the diaphragm and the external intercostals. During active breathing due to increased metabolic demand (hyperpnea), for example, during exercise, exhalation becomes more active and the abdominal and internal intercostal muscles are contracted to push the air out of the lungs (see Figure 2.1B). However, active expiration also plays a critical role in various voluntary and emotional behaviors such as laughing, crying, or speaking. To aid in these processes, the incoming and outgoing airflow is further regulated by the various valve muscles that can adjust the resistance of the upper airways (see Figure 2.1C; for review see Krohn et al., 2023).

During respiration, gas exchange takes place in the ~300 million alveoli present in the human lungs, adding up to a gas exchange surface of ~70 m^2. At this surface, ~250 ml O_2 is taken up and ~200 ml CO_2 is released each minute to maintain homeostasis. The O_2 and CO_2 content in the blood is monitored by both peripheral and central chemosensors in the brainstem, more specifically in the ventral parafacial nucleus (a region also known as the retrotrapezoid nucleus), which detect and respond to fluctuations in CO_2 and pH in the cerebrospinal fluid. Mechanoreceptors, on the other hand, sense the status and changes in pump muscles and the lungs and relay this information via the vagus nerve. All of this information is relayed to the preBötzinger Complex (preBötzC) to regulate breathing to facilitate optimal gas exchange in the lungs. Whereas this automatic control of breathing takes place in the medulla, the voluntary control system is located in the primary motor region of the cerebral cortex and communicates with the respiratory motor neurons via the corticospinal tracts (Barrett et al., 2019a).

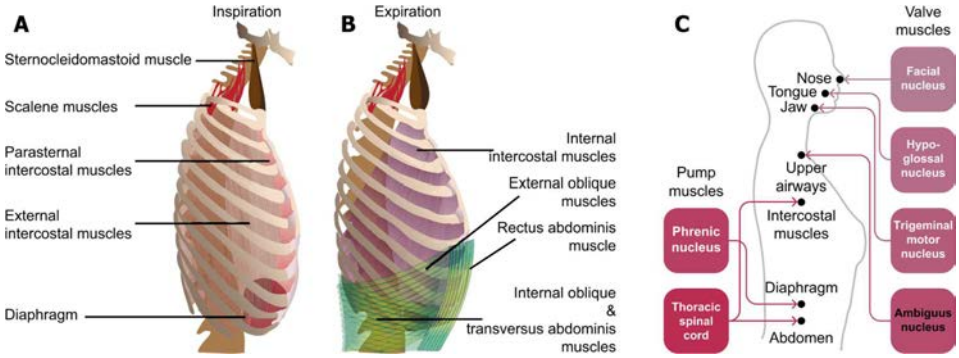

Figure 2.1. Respiratory muscles and their innervation. A) Muscles orchestrating inhalation, where the diaphragm and the external intercostal muscles are the main driving force, but the other muscles can also contribute to enlarging the chest. **B)** Muscles involved in active expiration, driven by the internal intercostal and the abdominal muscles. **C)** Innervation of the pump and valve muscles. Adapted from Krohn et al., 2023, under a CC-BY license.

2.1.2 Orchestration of the breathing cycle

Breathing is a rhythmic activity. This rhythm is generated by the preBötzC, a microcircuit of both excitatory and inhibitory interneurons located in the ventrolateral medulla (Smith et al., 1991). The breathing cycle can be broken down into different phases, most commonly inhalation and exhalation. Different parts of the breathing cycle are controlled by various parts of the brain (see Figure 2.2A). Neuronal activation of the preBötzC signals to inspiratory pump muscles to start inhalation (Del Negro et al., 2018).

The transition from inhalation to exhalation has shown to be influenced by the Kölliker-Fuse nucleus, with most neurons firing during inhalation and suddenly ceasing activation at the end of inhalation, marking the inhalation to exhalation transition (see Figure 2.2B; Damasceno et al., 2014; Dutschmann et al., 2021). The Kölliker-Fuse nucleus receives input from (among others) both the preBötzC and the Bötzinger complex, as well as from several central chemoreceptor areas (McGovern et al., 2015; Silva et al., 2016; Yang & Feldman, 2018). In turn, the Kölliker-Fuse nucleus has excitatory projections to many respiration areas, importantly the preBötzC, the postinspiratory complex, and the lateral parafacial nucleus (Biancardi et al., 2021; Oliveira et al., 2021; Yang et al., 2020).

It is thought that during active expiration, the lateral parafacial nucleus generates the expiratory rhythm (see Figure 2.2A), whereas normally only the preBötzC is active and generates the inspiratory rhythm (Huckstepp et al., 2016).

A third respiration phase is often present between in- and exhalation, so-called post-inspiration. During post-inspiration, the contraction of the diaphragm is extended, and laryngeal muscles are activated to slow expiratory airflow. It has been proposed that postinspiratory activity is generated by an excitatory network located medial to the parafacial nucleus and the VII nucleus, which has been named the postinspiratory complex (Anderson et al., 2016). However,

the existence of this complex is still under contention (Hülsmann, 2021). The Bötzinger complex consists mostly of inhibitory neurons and seems to be involved in the inhibition of the inspiratory activity generated by the preBötzC, as well as the suppression of the lateral parafacial nucleus during breathing at rest. As such, the neurons of the Bötzinger complex have mostly been found to be active during post-inspiration and exhalation (Ausborn et al., 2018; Flor et al., 2020; Marchenko et al., 2016).

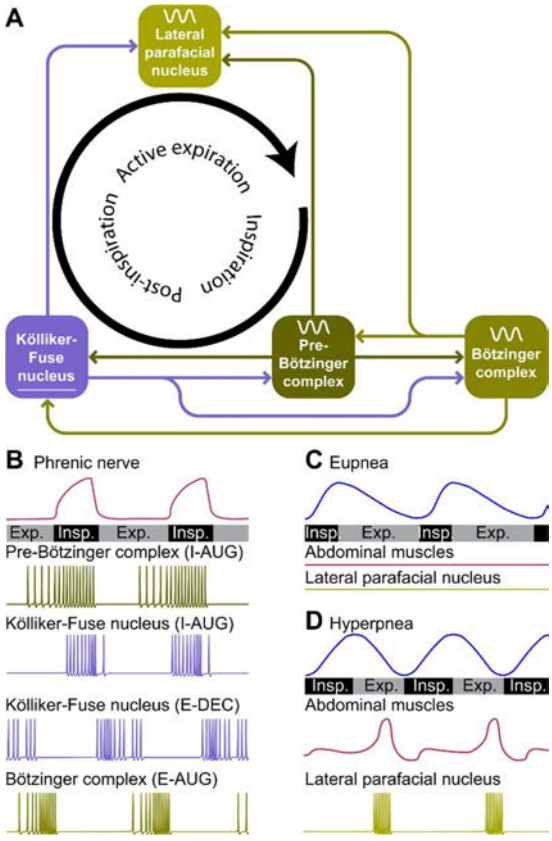

Figure 2.2. Central pattern generators encode the respiratory rhythm. A) Connections between the preBötzinger complex that organizes inspiration, the Kölliker-Fuse nucleus that relates to the inspiration/expiration switch, the lateral parafacial nucleus that triggers active expiration, and the Bötzinger complex related to expiration. **B)** Neuronal activity in the central pattern generators varies during the respiratory cycle. The schematized traces represent action potential firing of selected neuronal cell types in relation to activity of the phrenic nerve that drives the main inspiratory pump muscle, the diaphragm. From top to bottom: augmenting inspiratory neurons (I-AUG) from the preBötzinger complex and the Kölliker-Fuse nucleus, a decreasing expiratory neuron (E-DEC) from the Kölliker-Fuse nucleus, and an augmenting expiratory neuron (E-AUG) from the Bötzinger complex. **C)** During eupnea, thus, in the absence of active expiration, neither the expiratory pump muscles of the abdomen, nor the neurons of the lateral parafacial nucleus are active. **D)** During hyperpnea, thus when active expiration takes place, abdominal expiratory pump muscles are active when the lateral parafacial nucleus neurons produce action potentials. Insp.=inspiration, Exp.=expiration. Reproduced from Krohn et al., 2023 under CC-BY license.

Whereas this covers the basic aspects of the physiology of breathing and the respiratory cycle, breathing is a very complex activity and this introduction only scratches the surface. For the interested readers I highly recommend two excellent reviews that have informed much of what is written above and that go into much greater depth on the physiology of breathing (Del Negro et al., 2018; Krohn et al., 2023).

2.2 How breathing can influence brain activity

Besides fulfilling a physiological role, recent research has indicated that breathing modulates brain activity. In the following section I will highlight some of the pathways that have been proposed to explain how breathing can influence brain activity, and thereby behavior, perception, cognition, and emotion.

2.2.1 An evolutionary perspective

Evolutionary, olfaction is the oldest mammalian sensory system, and it developed as part of the respiratory system (Hsia et al., 2013; Rae & Koppe, 2004). Early mammaliaforms were, and modern rodents still are, restricted in their respiration to the nasal pathway, causing respiration and olfactory perception to coincide during evolution (Crompton et al., 2017; Trabalon & Schaal, 2012). Early on, the mammalian brain differed from its closest relatives in its high-resolution olfactory perception, necessary for survival by aiding in processes such as spatial navigation (Jacobs, 2012). It has been proposed that the evolution of the modern, large and highly encephalized mammalian brain was driven by the need to process this olfactory information (Rowe et al., 2011). While the sensory structures of the mammalian brain have generally evolved to scale with the body size of the animal, the proportionally large olfactory bulb (OB) is the exception (Finlay et al., 2011; Reep et al., 2007; Yopak et al., 2010). Critically, it has been hypothesized that the early evolutionary link between brain growth and the olfactory/respiratory systems shaped perceptual processes in all sensory systems to be upregulated by, and rhythmically locked to, the inhalation phase of breathing to better prepare the animal for all types of incoming sensory stimuli (Heck et al., 2017; Perl et al., 2019). Thus, this evolutionary pathway has been hypothesized to have created a direct link between respiration and oscillatory rhythms throughout the cerebral cortex (Fontanini & Bower, 2006).

2.2.2 The olfactory bulb and what we have learned from chemosensory research

Much of what we know about the respiratory influence on neural dynamics has its origin in the chemosensory community. Given that airflow heavily influences exposure to olfactory, taste, and trigeminal stimuli, the interest in respiration in this field is not surprising. Particularly the olfactory community has been interested in the dynamics of respiration and sniffing to better understand how the olfactory sense works (see for example Buonviso et al., 2006; Kay, 2005, 2014; Kepecs et al., 2006; Sobel et al., 1998; Wachowiak, 2011). Lord Adrian's pioneering work in the mid-20th century demonstrated respiration-related oscillations (RROs) in the local field potentials of the OB (Adrian, 1942, 1950, 1951). These RROs in the OB have since then been confirmed (Macrides & Chorover, 1972; Onoda & Mori, 1980; Ravel & Pager, 1990), and shown to be produced within the OB, rather than being transferred from other brain regions (Adrian, 1950; Ottoson, 1960). The OB has a prominent role in olfaction, being the first central olfactory structure and having a function both in initial processing of incoming olfactory information and projecting this information to further downstream parts of the olfactory system. The OB receives its input from olfactory sensory neurons (OSNs) located in the olfactory epithelium, at the roof of the nasal cavity. Smells are detected by odor molecules

binding to, and activating OSNs, which in turn leads to activation of the OB. The RROs in the OB fulfill a function, as they have been shown to aid olfaction by preparing the OB for incoming olfactory stimuli (Kay, 2015; Kay et al., 2009). Since lord Adrian's discoveries, respiration-related activity has been found all along the olfactory pathway, starting with oscillatory responses in the olfactory epithelium synchronized to respiration during odor presentation (Chaput, 2000), and respiration-locked activity of individual OSNs both with, and without odors present (Duchamp-Viret et al., 2005). Once the signal reaches the OB, the mitral and tufted cells have been found to fire in rhythm with respiration (Buonviso et al., 1992; Chaput & Holley, 1980; Cury & Uchida, 2010; Macrides & Chorover, 1972). In addition, faster beta and gamma oscillations have also been shown to be phase-locked to particular parts of the respiratory cycle (Buonviso et al., 2003; Cenier et al., 2009; Freeman, 1978; Freeman & Schneider, 1982; Manabe & Mori, 2013). Much work has been done on how the OB is influenced by respiration and for a review I recommend the work of Buonviso et al. (2006). Further downstream in the olfactory system, local field potential oscillations coupled to respiration have also been found in the piriform cortex. Again, showing an influence of respiration on both slow (Biskamp et al., 2017; Bressler, 1984, 1987; Fontanini & Bower, 2005) and fast rhythms (Fontanini et al., 2003; Freeman, 1959; Gonzalez et al., 2023; Litaudon et al., 2003; Neville & Haberly, 2003). Furthermore, burst activity linked to respiration is also present in the piriform-amygdala region (Onimaru & Homma, 2007).

Although most of the early studies on the respiratory influence on brain oscillations in the olfactory system used odor stimulations, the respiratory influence was also present in several instances without odor presentations. Early on, Adrian and Ludwig (1938) suggested that a mechanical activation of the olfactory system by nasal airflow might be behind this respiratory influence. Ueki and Domino provided some evidence for this hypothesis in dogs and monkeys by showing that the olfactory nerve might be sensitive to mechanical stimulation (Ueki & Domino, 1961). Later, Sobel et al. (1998) showed that human sniffing behavior could activate the piriform cortex in the absence of odors and hypothesized that the human olfactory nerve might be sensitive to mechanical stimulation. Finally, the source of this hypothesized mechanical sensitivity in the olfactory system was proven when it was discovered that OSNs respond not just to chemicals, but also to mechanical stimuli (Grosmaitre et al., 2007). This is thought to explain the mechanism behind RROs in the OB. Specifically, the pressure of inhaled air activates OSNs, which in turn project this information to the OB where it causes local field potentials at the respiration frequency (Kay et al., 2009). Later, more details came forward with the discovery that the mechanical sensitivity of OSNs is mediated through the G protein-coupled odorant receptors, present in some, but not all types of olfactory receptors (Connelly et al., 2015; Wu et al., 2017). After this discovery of the mechanosensitivity of OSNs, interest in respiratory coupled brain oscillations spread beyond the chemosensory community, really kicking off with evidence of respiration-locked neuronal oscillations in the OB as a driving force behind neuronal oscillations in the somatosensory cortex of mice (Ito et al., 2014). Since then, the existence of respiratory-brain coupling has been shown in many brain areas beyond the olfactory systems, including the medial prefrontal cortex (Biskamp et al., 2017;

Folschweiller & Sauer, 2021a), the hippocampus (Lockmann et al., 2016; Lockmann & Tort, 2018; Nguyen Chi et al., 2016; Yanovsky et al., 2014), parietal cortex (Jung et al., 2022; Tort et al., 2021; Zhong et al., 2017), orbitofrontal cortex (Kőszeghy et al., 2018), and the prelimbic cortex (Moberly et al., 2018; Zhong et al., 2017).

More recently, respiration-locked activity has also been found in widespread cortical and limbic areas in humans (Heck et al., 2016; Herrero et al., 2018; Kluger & Gross, 2020; Zelano et al., 2016). These RROs are not limited to the slow respiration frequency, but in a process called cross-frequency phase-amplitude coupling, these slow waves can also modulate the amplitude of faster neural oscillations (Fontanini & Bower, 2006; Ito et al., 2014). While some of these RROs might also originate from the central pattern generators in the brainstem (see the next section), many studies have shown that respiration entrained brain oscillations disappear upon removal of the OB, the OSNs, or diversion of airflow from the nose to the mouth via tracheotomy (Fontanini et al., 2003; Ito et al., 2014; Lockmann et al., 2016; Ravel & Pager, 1990; Yanovsky et al., 2014; Zhuang et al., 2019). These findings prove that the OB is a major, though not the sole, player when it comes to respiratory entrained neural oscillations at both low and high frequencies in brain regions related to olfaction, cognition, and mood (see Figure 2.3, and for recent reviews see Brændholt et al., 2023; Folschweiller & Sauer, 2021b, 2022; Heck et al., 2022; Nakamura et al., 2023).

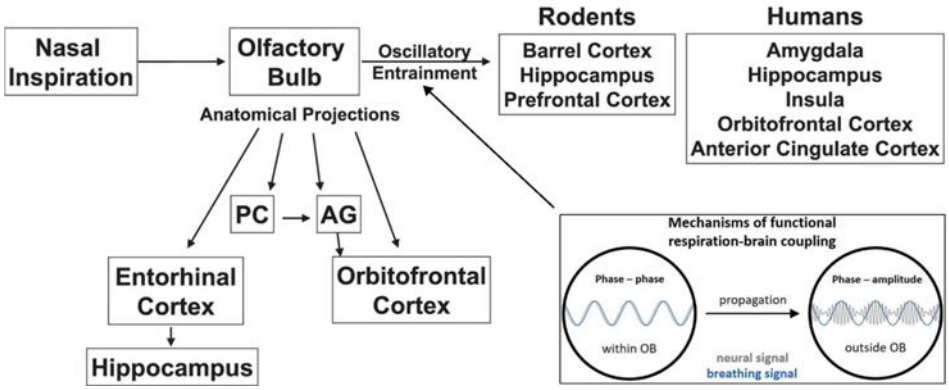

Figure 2.3. How breathing entrains neural oscillations via the olfactory bulb. Relevant anatomical projections of the olfactory bulb and further brain areas in which respiratory-entrained neural oscillations have been found. In the bottom right you see a schematic depiction of phase-amplitude coupling via which slow respiratory cycles can modulate the amplitude of higher-frequency brain oscillations. Abbreviations: PC, piriform cortex, AG, amygdala, OB, olfactory bulb. Adapted with permission from (Brændholt et al., 2023; Maric et al., 2020) under CC-BY license and CCC license number: 5641360130759.

2.2.3 The brainstem and the locus coeruleus – norepinephrine pathway

In an earlier section I introduced how the preBötzC is the main central pattern generator, orchestrating the inspiratory rhythm to meet metabolic demands. This collection of interneurons located in the ventrolateral medulla of the brain stem sends direct excitatory and inhibitory projections to distinct targets throughout the brain (see Figure 2.4), the activation of which is thought to be modulated by inspiration (Yang & Feldman, 2018). Among these brain regions that the preBötC sends projections to is the locus coeruleus (LC), a cell cluster in the pons that is the main producer of norepinephrine (NE) in the brain. The LC has a well-established role in many cognitive functions, including arousal and memory, and has projections all over the brain, among which are strong connections to the hippocampus and projections to the OB (Sara, 2009, 2015). Excitatory inputs to the LC from the preBötC have been found to be phase-locked to inspiration, causing a respiration regulated release of NE in the LC (Yackle et al., 2017). It has been proposed that the preBötC – LC circuit enables the respiratory center to directly communicate with and control higher-order brain structures and thereby influence behaviors such as arousal, memory, attention, and olfactory processing (Melnychuk et al., 2018, 2021; Yackle et al., 2017). The importance of these connections was shown when the ablation of the projections from the preBötC to the LC in mice led to changes in the balance between calm and arousal behaviors in the animals, without affecting their breathing (Yackle et al., 2017). In addition, the preBötC has projections to the central medial thalamus, which in turn is directly connected to the limbic and sensorimotor cortical areas (Kang et al., 2018). Overall, these efferent projections potentially allow the preBötzC to go beyond generating and modulating the breathing pattern to coordinate breathing with other behaviors, physiology, cognition, or emotional state (Yang & Feldman, 2018).

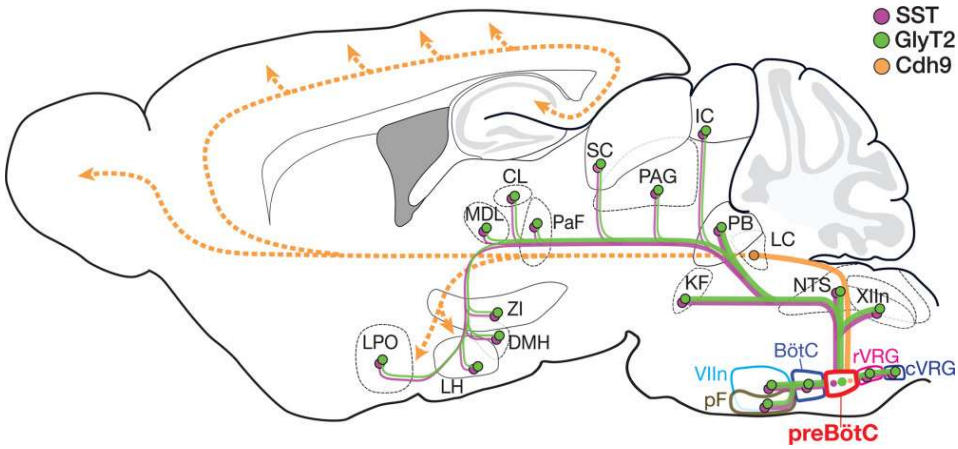

Figure 2.4. Projections from the preBötzinger complex in the rodent brain. Projections from three types of preBötzinger Complex neurons to various brain regions, as well as the indirect projections via the LC (dotted yellow line). Abbreviations: BötC, Bötzinger Complex; Cdh9, neurons that express the molecular marker Cdh9; CL, central medial thalamus; cVRG, caudal ventral respiratory group; DMH, dorsomedial hypothalamus; GlyT2, neurons expressing the glycine transporter GlyT2; IC, inferior colliculus; KF, Kölliker Fuse; LC, locus coeruleus; LH, lateral hypothalamus; LPO, lateral preoptic area; MDL, medial dorsal thalamus; NTS, nucleus of the solitary tract; PaF, parafascicular thalamus; PAG, periaqueductal gray; PB, parabrachial nuclei; pF, parafacial nucleus; rVRG, rostral ventral respiratory group; SC, superior colliculus; SST, somatostatin expressing neurons; VIIn, facial nucleus; XIIn, hypoglossal nucleus; ZI, zona incerta. Reproduced with permission from (Yang & Feldman, 2018). CCC license number: 5640841192791.

2.2.4 Additional pathways

While the pathways via the OB and the brainstem breathing pattern generators are the most well researched and also play the biggest role in my research, I want to take a brief moment to mention that additional pathways have been suggested as mechanisms for respiratory influences on brain activity. Breathing creates, for example, a lot of somatosensory information in the form of lung movement that is relayed to the brain via the vagus nerve and intermediate nuclei in the brainstem and can influence hippocampal activity (Kim et al., 2022; Radna & MacLean, 1981). Furthermore, information about diaphragm and chest movement is relayed via the phrenic nerve to the somatosensory cortex (Davenport et al., 2010; Nair et al., 2017). Similarly, interoceptive information such as air hunger and respiratory effort are signaled to the brain via the vagus nerve and brainstem nuclei, up to interoceptive regions such as the insular cortex (Craig, 2002; Garfinkel et al., 2016; Nikolova et al., 2022). In addition, the cardiac and the respiratory systems are tightly coupled, as they play a complementary role in providing the body with oxygen and releasing carbon dioxide. Breathing has been shown to influence key aspects of the heart rhythm, causing phenomena such as respiratory sinus arrhythmia, and cardioventilatory coupling (for review, see Elstad et al., 2018). In turn, the cardiac system can relay information from the heart to the brain via baroreceptors, potentially

targeting the insular cortex (Saper, 2002). Furthermore, oscillations in blood flow are likely to impact specific brain regions (Liang et al., 2013). This provides an additional pathway via which breathing could indirectly influence brain oscillatory activity (for review, see Maric et al., 2020; Parviainen et al., 2022). Figure 2.5 presents all major breathing pathways that are believed to shape brain activity.

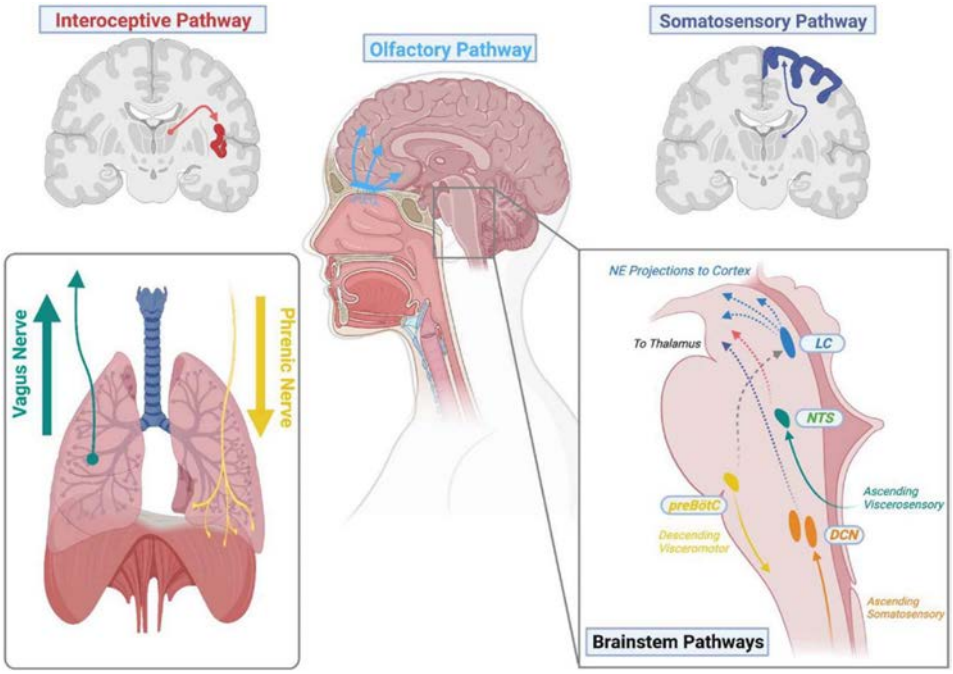

Figure 2.5. Major neuroanatomical pathways that potentially shape respiration-brain coupling. Respiratory rhythms can constrain brain function by at least three interacting neuroanatomical pathways. At each respiratory cycle, descending motor signals originating in the pre-Bötzinger complex (preBötC) are carried to the lungs and diaphragm via the phrenic nerve, eliciting muscular contraction and relaxation. Each breath then drives rhythmic olfactory, somatosensory, and interoceptive signals which are communicated to the brain via the olfactory bulb, somatosensory, and vagal nerves, respectively. The mechanical ventilation of the lungs induces regular somatosensory rhythms in the chest wall, head, and bodily posture, which are relayed by the dorsal column nuclei (DCN) to engage beta oscillations in the primary somatosensory cortex and cerebellum, synchronizing sensorimotor rhythms with the breath. In the brainstem, a complex predictive control loop between the various respiratory nuclei integrates ascending viscerosensory and descending visceromotor signals to maintain respiratory homeostasis. This loop also directly engages the locus coeruleus (LC), linking respiratory cycles to global noradrenergic (NE) gain control (shown in blue). The rhythmic fluctuation of homeostatic variables such as air hunger and respiratory effort is relayed to the nucleus tractus solitarius (NTS) of the brainstem by the ascending vagus (pathway in green), before being transmitted to higher interoceptive regions such as the insular cortex (illustrated in red). Reproduced with permission from (Allen et al., 2023) CCC License Number: 5637571226936.

2.2.5 Gaps in the literature

Much of what we know about respiratory-driven brain oscillations comes from animal research, particularly from rodents. While the main respiratory mechanics and structures are very similar across mammals, there are some important differences that should be considered when trying to translate findings of respiratory influences on brain activity in rodents to humans.

First of all, rodents are obligate nose-breathers, meaning they cannot naturally breathe through their mouth (Gautam & Verhagen, 2012). Therefore, mouth breathing has rarely been investigated in animals, and usually has only served as a control condition to divert airflow from the nose by blocking the nostrils or invasive tracheotomy. Humans, on the other hand, breathe via their nose and mouth, both voluntarily and automatically, and readily use both routes simultaneously during speech (Lester & Hoit, 2014; Pleil et al., 2021).

Secondly, much of the research on respiratory influences on brain activity in both animals and humans has reported effects linked to particular phases of the breathing cycle. This is unsurprising, given the different airflow mechanics and brain regions involved at different parts of the breathing cycle. However, it is important to note that:

- It is still unclear exactly which brain areas are involved in which part of the respiratory cycle, and there is still debate about the phases of the breathing cycle itself (for review, see Krohn et al., 2023).
- Airflow mechanics across the respiratory cycle differ between rodents and humans. In humans, both inhaled and exhaled air passes over the olfactory epithelium, but this is not the case in rodents and canines (Craven et al., 2009; Yang et al., 2007; Zhao et al., 2004, 2006). This difference in airflow mechanics may lead to differences between humans and rodents in the timing of mechanical activation of OSNs.
- Rodents breathe at a much higher frequency than humans, with mice breathing approximately 10-20 times faster (see Figure 2.6). This difference in breathing frequency raises the question of whether phase-amplitude coupling between the breathing rhythm and higher frequency brain rhythms that have been found in animal studies (González et al., 2022) can be expected to occur at similar frequencies in humans.

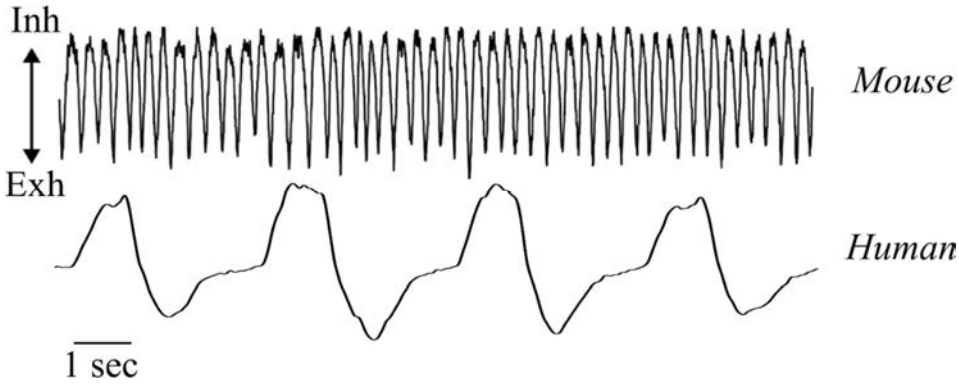

Figure 2.6 Breathing rates of mice and humans. The above shows the respiration trace of a head-fixed mouse. Generally, mice breathe at a frequency of approximately 2 to 5 Hz at rest. Below shows the respiration trace of a seated human at rest. Generally, humans breathe at a frequency of approximately 0.2 to 0.25 Hz at rest. Inh = inhalation, Exh = exhalation.

In addition to these limitations, animal research on respiratory-brain coupling varies greatly in which motoric and conscious state the animal being investigated is in, i.e., whether they are head-fixed, freely moving, at rest, or anesthetized. Differences in activity have been shown to influence the extent of respiratory-brain coupling (Folschweiller & Sauer, 2023). For example, interactions between nasal respiration and activity in the OB, piriform cortex, and hippocampus, have been found to be stronger during exploratory foraging behavior than during rest (Sheriff et al., 2021). Additionally, respiratory long-range gamma synchrony modulation during awake states decreases during sleep (González et al., 2022). Furthermore, slower synchronization frequency (delta oscillations) has been found during immobility, compared to faster synchronization frequency (theta oscillations) during exploratory behavior (Biskamp et al., 2017; Zhong et al., 2017). Due to technical limitations of neuroimaging recording methods, human experiments on respiratory-brain coupling have only been performed in immobile settings. This limits our understanding of potential respiratory neural influences while freely moving and exploring environments.

Further limitations are imposed by the ethical need for neuroimaging methods in humans to be non-invasive. This has limited direct recordings from the OB, an important structure in this line of research. Until now only three studies have made intracranial recordings in relation to breathing, obtained from treatment-resistant epilepsy patients, and only one of these recorded signals from the OB (Herrero et al., 2018; Nobis et al., 2018; Zelano et al., 2016). This is in stark contrast to the animal literature, where direct recordings from the OB are common and allow for a much more direct look into the intricacies of RRO and their propagation throughout the brain. This lack of non-invasive methods to record activity from the OB has restricted our ability to confirm the results of animal studies in humans. However, recent developments indicate that OB recordings from humans might become more frequent and allow us to resolve some of these issues. Iravani and colleagues demonstrated successful non-invasive recordings of OB activity during olfactory tasks in humans using a newly developed EEG method called

the electrobulbogram (Iravani et al., 2020). Additionally, advances in magnetic resonance imaging (MRI) show potential for obtaining functional signals from the human OB with the use of a special surface coil (Fournel et al., 2020), or with the use of 7T MRI in combination with Transverse Relaxation Time (T2) whole-brain preparation (Miao et al., 2021).

2.3 Breathing and pupil size

2.3.1 Pupil size modulation mechanisms and pathways

Changes in pupil size are thought to reflect internal brain states (Schwalm & Jubal, 2017), but also directly affect visual perception, with pupil dilation leading to higher sensitivity for faint stimuli and pupil constriction providing sharper acuity. Consequentially, any potential respiratory effects on pupil dynamics are of considerable interest and significance. This raises the fundamental questions of how pupil size is regulated and how respiration might exert an influence on this mechanism.

Pupil size constantly needs to be adjusted to the variations in light intensity of our environment to regulate the amount of light that enters our eyes. Pupil dilation is controlled by the radial dilator muscle of the iris, which is enervated by sympathetic axons from the superior cervical ganglion located in the neck region, anterior to the C1-4 vertebrae. The superior cervical ganglion receives input from the intermediolateral cell column (IML) of the spinal cord (Kardon, 2005; Samuels & Szabadi, 2008).

In contrast, pupil constriction, is controlled by the sphincter muscle of the iris, which, via the ciliary ganglion, is enervated by parasympathetic axons of cholinergic neurons from the Edinger-Westphal nucleus (EWN) located in the midbrain (Horn et al., 2008; Kuchiiwa et al., 1989; Samuels & Szabadi, 2008; Strassman et al., 1987). Changes in light levels are registered and conveyed by photosensitive retinal ganglion neurons that contain melanopsin, and project to the pretectal olivary nucleus in the midbrain (Berson et al., 2002; Gamlin et al., 2007; Hattar et al., 2002). This presents the first of three major pathways found to regulate pupil size.

This parasympathetic pathway with its photosensitive neurons is mostly responsible for the pupillary light reflex (i.e. pupillary constriction in response to light see Figure 2.7A).

The second pathway modulating pupil size goes via the superior colliculus, and is more complex, containing both a direct and an indirect branch (see Figure 2.7). Superficial layers of the superior colliculus receive direct input from retinal ganglion neurons, and project to intermediate layers of the superior colliculus. Some of the neurons of the intermediate layers of the superior colliculus project directly to the EWN and can thereby influence the parasympathetic pupil size modulation (Huerta & Harting, 1984). Additional control of the parasympathetic pathway comes from the intermediate layers of the superior colliculus neurons that indirectly project to the EWN via the mesencephalic cuneiform nucleus (May et al., 2016).

However, the mesencephalic cuneiform nucleus also projects to the thoracic and cervical spinal cord, thereby exerting a sympathetic influence on pupil size (Verberne, 1995).

This second pathway is thought to be involved in mediating pupil changes caused by orienting and saliency responses (for review see Joshi & Gold, 2020). However, much of this second pathway is still unknown, and more research is needed to clarify how pupil size is modulated via this pathway (McDougal & Gamlin, 2014).

Finally, the third pathway is probably the most studied of the three presented here, the locus coeruleus (LC) – norepinephrine (NE) pathway. Because the LC is the main NE producer in the brain, it can influence a wide range of processes via its adrenergic projections, including the modulation of pupil size. The LC has an excitatory sympathetic influence via its direct projections to adrenergic receptors on the IML (Liu, Rodenkirch, et al., 2017; Szabadi, 2018; Westlund & Dan Coulter, 1980). Additional, indirect sympathetic influence from the LC, comes from its reciprocal connections with the hypothalamus, which itself has projections to the IML (Nunn et al., 2011; Szabadi, 2018). Furthermore, the LC can also exert a parasympathetic influence via its direct projections to the superior colliculus, and via its ability to modulate neural activity in the EWN (see Figure 2.7; Breen et al., 1983; Szabadi, 2018). It is thought that via this pathway, generally, activation of the LC leads to a decrease of the parasympathetic drive via inhibition of the EWN, and an increase of the sympathetic drive via activation of the IML, together causing the pupils to dilate (Breen et al., 1983; Joshi et al., 2016; Liu, Rodenkirch, et al., 2017).

This third pathway is thought to be the main cause of changes in pupil size due to cognitive demands or arousal (Alnæs et al., 2014; Aston-Jones & Cohen, 2005; Mathôt et al., 2013).

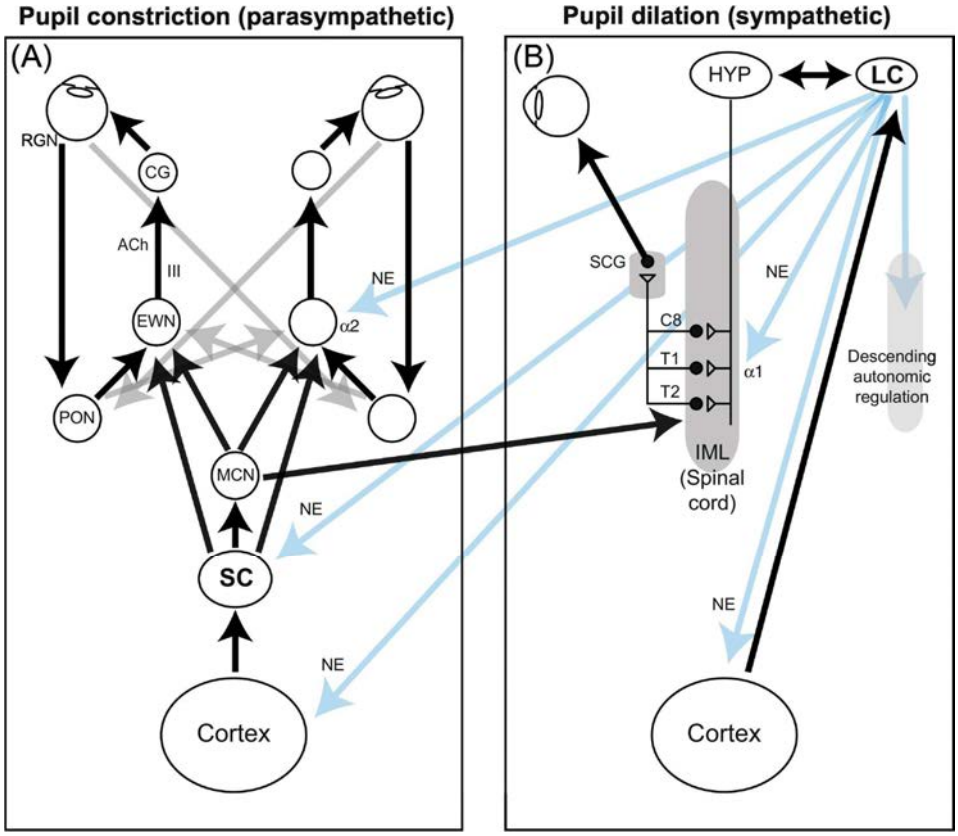

Figure 2.7. Neural pathways controlling pupil constriction and dilation. Gray arrows indicate hemisphere-crossing connections at the level of the brainstem. Blue arrows indicate locus coeruleus (LC) output to the brainstem and cortex. C8, T1, and T2 refer to segments of the intermediolateral cell column (spinal cord). Abbreviations: ACh, acetylcholine; CG, ciliary ganglion; EWN, Edinger–Westphal nucleus (midbrain); HYP, hypothalamus; III, third cranial nerve; IML, intermediolateral cell column; MCN, mesencephalic cuneiform nucleus; NE, norepinephrine; PON, pretectal olivary nucleus (midbrain); RGN, retinal ganglion neuron; SC, superior colliculus; SCG, superior cervical sympathetic ganglion. Reproduced with permission from (Joshi & Gold, 2020), CCC license number: 5643081478353.

While our understanding of the three primary pathways involved in pupil size modulation remains incomplete, it should be noted that additional pathways have been proposed to play a role in this process as well (for a comprehensive review, refer to Joshi & Gold, 2020). However, in this context, it is crucial to emphasize the significance of the third pathway, which centers on LC activity and its adrenergic projections. This pathway holds particular interest for my work as it offers a plausible explanation for the documented respiratory-driven fluctuations in pupil size.

As discussed earlier, the preBötzC has excitatory projections to the LC, leading to rhythmic activation of the LC in pace with the breathing frequency (Yackle et al., 2017). Furthermore, the LC is chemosensitive to CO_2 levels and has been found to regulate the respiratory rhythm upon detecting excessive CO_2 levels (hypercapnia; Biancardi et al., 2008; Hilaire et al., 2004; Quintero et al., 2017), potentially doing so via its direct projections to the preBötzC (Liu et al., 2021).

In turn, changes in pupil size have been demonstrated to be highly correlated with activity in the LC in both animals and humans (Murphy et al., 2014), with stimulation of the LC resulting in the dilation of the pupils after a short delay (Joshi et al., 2016). Therefore, pupil size has been used as a marker of LC activity (Alnæs et al., 2014; Aston-Jones & Cohen, 2005; Grueschow et al., 2020; Liu, Rodenkirch, et al., 2017). To sum up, one of the major pathways controlling pupil size has been found to be modulated by the respiratory rhythm, providing a pathway for respiration to influence pupil size.

2.3.2 Experimental evidence for respiratory influences on pupil size dynamics

The prevailing belief that inhalation causes pupil dilation and exhalation leads to pupil constriction is widely acknowledged (Ashhad et al., 2022). Despite this longstanding assertion, dating back to studies like Borgdorff (1975) and Golenhofen & Petrányi (1967), research on respiratory effects on pupil dynamics in humans has remained relatively limited. While pupil size has frequently been employed as an indicator of internal states in various experiments (Schwalm & Jubal, 2017), the specific respiratory interactions with pupil dynamics have not been extensively investigated.

There are four studies directly investigating and finding an effect of breathing phase on pupil size dynamics (Golenhofen & Petrányi, 1967; Kaulen et al., 1979; Melnychuk et al., 2021; Nakamura et al., 2019). Furthermore, two studies have investigated the effect of breathing depth on pupil size dynamics and found that the amplitude of pupil size fluctuations correlated with the breathing depth, and that slow deep breathing led to a general decrease in pupil size (Ohtsuka et al., 1988), whereas deep breathing was also found to increase pupillary unrest (Schumann et al., 2020). Finally, six studies have investigated the effect of breathing rate on pupil size dynamics, three studies found an influence of respiratory rate (Calcagnini et al., 2000; Daum & Fry, 1981; Yoshida et al., 1994), while the other three studies did not (Bouma & Baghuis, 1971; Schumann et al., 2015, 2020). The evidence for an influence of respiratory rate on pupil size dynamics comes from the findings of peaks in the power spectrum of the pupil size measurements, around the breathing frequency (Calcagnini et al., 2000; Daum & Fry, 1981; Yoshida et al., 1994). This was also discovered in a further study during a memory search task; however, the respiratory peak in the pupil power spectrum disappeared upon increased workload (Murata & Iwase, 2000). It is worth noting that the three studies that did not find an influence of respiration rate on pupil dynamics all had a significantly larger sample size than the studies that did find an effect.

Taken together, the experimental evidence for respiratory influences on pupil size dynamics in humans is weak (Schaefer et al., 2023). This is unexpected given the longstanding and pervasive dogma that associates pupil dilation with inhalation and pupil constriction with exhalation (Ashhad et al., 2022). Additionally, a potential neural pathway involving the LC-NE system has been identified as a candidate explanation for this effect. Nevertheless, a closer examination reveals several factors that might account for the discrepancies observed in studies investigating the influence of respiration on pupil size dynamics.

First and foremost, despite the enduring belief that inhalation leads to pupil dilation, this notion has also faced opposition. As far back as 1958, Irene Loewenfeld, a prominent figure whose extensive research forms the basis of much subsequent work in this field, expressed reservations about the widely held belief that inspiration drives increases in pupil size, suggesting that such claims lack substantiation (Loewenfeld, 1958).

Furthermore, Borgdorff's work, which has been the main source of evidence for respiratory-driven influences on pupil size, only showed this effect in lightly anesthetized cats (Borgdorff, 1975). The pupil dilations that were locked to the respiratory cycle disappeared when the animals were either deeply anesthetized or awake. Therefore, Borgdorff's findings do not provide strong evidence to claim that inhalation leads to dilated pupils in humans.

Additionally, although the LC-NE pathway plays a clear role in modulating pupil size, and pupil size has often been used as a proxy for LC activity, recent work has shown that pupil size modulation is complex and involves multiple pathways and neurotransmitters (Joshi & Gold, 2020). Indeed, the latest research has revealed that pupil size is not actually an accurate real-time measure of LC activity (Megemont et al., 2022).

While the LC-NE pathway is not the only source of pupil size modulation, respiratory areas are in turn not the only source of LC modulation (Luppi et al., 1995; Schwarz et al., 2015).

Moreover, considering the diversity of methods used in the few studies investigating respiratory influences on pupil size makes it clear why the seemingly simple question of whether respiration modulates pupil size is not actually that simple, and has still not been answered.

2.4 Breathing and visual perception

In addition to the historical claims regarding respiration's influence on pupil size, early claims also suggested a connection between respiration and visual perception. As far back as 1974, a study demonstrated that breathing phase impacted the probability of detecting faint, briefly presented stimuli. Specifically, it revealed a greater likelihood of detecting the stimuli during the exhalation phase (Flexman et al., 1974). The authors did not mention respiratory effects on pupil size as an explanation, instead they proposed the existence of an optimal physiological state during exhalation that enhances the detection of faint visual stimuli (Flexman et al., 1974).

We now know that respiration modulates neuronal oscillations in wide range of cortical and subcortical structures (Kluger & Gross, 2021; Zelano et al., 2016). Importantly, specific neuronal oscillations have been shown to be related to perception acuity. For example, the power of the alpha rhythm in the parieto-occipital area has been inversely related to the likelihood of detecting faint visual stimuli (Ergenoglu et al., 2004; Iemi et al., 2017, 2022; Iemi & Busch, 2018). Using this information, Kluger and colleagues then showed that pre-stimulus alpha power was modulated by the respiratory cycle, influencing visual perception ability. This demonstrates that optimal brain states for the detection of faint stimuli exist, and that respiration actively aligns the sampling of visual information with states of heightened perceptual ability (Kluger et al., 2021). It is interesting to note that contrary to the previous findings, this study showed improved perceptual performance during the inhalation, rather than the exhalation phase. This finding was later replicated and extended by a study showing that perceptual awareness and decision-making speed was increased during inhalation compared to exhalation, without affecting accuracy, for both nose and mouth breathing, in a visual near-threshold decision-making task (Molle et al., 2023).

However, conflicting evidence has been presented as well, as other behavioral studies have not found any effect of the respiratory phase on the ability to detect subtle visual stimuli based on whether the stimuli were presented during the inhalation or exhalation phase (Mizuhara & Nittono, 2022, 2023).

Moreover, studies have shown that humans tend to align experimental task onset (including those in visual tasks) with specific phases of the breathing cycle, and to the degree in which they do so successfully, they also improve their performance (Grund et al., 2022; Huijbers et al., 2014; Johannknecht & Kayser, 2022; Perl et al., 2019; Zelano et al., 2016). However, the studies which show that humans tend to align task onset to a certain part of the breathing cycle, are so far not consistent in their findings regarding which part of the breathing cycle is preferred for alignment.

Therefore, while a respiratory influence on neural excitability of the brain seems likely, the details of how our perception and cognition is influenced over the breathing cycle are yet to be determined.

2.5 Breathing and memory

The first notion that respiration could potentially influence memory functions came from the observation that in rabbits, cats, rats, and mice, the breathing frequency overlaps with the hippocampal theta rhythm (4-10 Hz), which is heavily involved in memory processes (Buzsáki, 2002; Gordon, 2011). It is thought that the hippocampus communicates with other brain structures related to memory (such as the prefrontal cortex (Colgin, 2011; Jones & Wilson, 2005; Preston & Eichenbaum, 2013)) via theta-band coherence (DeCoteau et al., 2007; Popa et al., 2010; Sirota & Buzsáki, 2005). Furthermore, it has been shown that hippocampal theta

oscillations are directly involved in the encoding and retrieval processes of memory (Douchamps et al., 2013; Kragel et al., 2020; Lever et al., 2010; Manns et al., 2007; Newman et al., 2013; Siegle & Wilson, 2014). Early support for the idea that the breathing rhythm can influence hippocampal theta came from the observed coupling between hippocampal theta and nasal respiration in hamsters during exploratory behavior (Macrides, 1975). Later on, OB respiratory oscillations were found locked to hippocampal theta rhythms in rats while they were performing an odor discrimination task with a memory component. Interestingly, the performance of the rats was positively correlated with the coherence magnitude between the OB and hippocampal theta frequencies (Kay, 2005). Despite the fact that humans breathe at a much slower pace of ~0.16-0.33 Hz, and therefore their breathing rhythm does not overlap with the theta frequency, experimental research has shown that also in humans hippocampal theta power varies in phase with respiration and is amplified during inhalation (Zelano et al., 2016). Besides this intrinsic theta rhythm of the hippocampus, slightly slower (2-4 Hz), respiration locked theta oscillations were discovered in the hippocampus of rats and mice (Lockmann et al., 2016; Lockmann & Tort, 2018; Chi et al., 2016; Yanovsky et al., 2014). This respiration-locked theta rhythm differed from the intrinsic hippocampal theta rhythm in an important manner, namely in the ability to modulate the amplitude of hippocampal gamma oscillations via phase-amplitude coupling (Biskamp et al., 2017). The respiratory modulation of gamma power has since then also been found in the neocortex of rats (Rojas-Líbano et al., 2018), cats (Cavelli et al., 2020), and even in the hippocampus and frontal cortex of humans (Herrero et al., 2018).

Generally, gamma oscillations in the hippocampus occur at specific phases of theta oscillations in a process called cross-frequency coupling (Bragin, Jando, Nadasdy, Hetke, et al., 1995; Canolty et al., 2006; Colgin, 2016; Nakazono et al., 2018). Intracranial EEG studies have shown that working memory in humans is dependent on hippocampal theta-gamma cross-frequency coupling (Axmacher et al., 2010) and the strength of theta-gamma coupling in rodents during learning is directly correlated with performance accuracy in memory recall (Tort et al., 2009).

A third hippocampal rhythm involved in memory processes are sharp wave ripples (SWR). These brief (~100 ms), high-frequency (150-300 Hz) hippocampal oscillations are thought to support spatial memory formation and the process of memory consolidation and retrieval (Buzsáki, 2015; Fernández-Ruiz et al., 2019; Girardeau et al., 2014; Jadhav et al., 2012; Joo & Frank, 2018). It has been suggested that SWR aid these memory functions by being involved in the replaying of memory-related information, and by transferring memories initially stored in the hippocampus to the neocortex (Buzsáki, 2015; Jadhav et al., 2012). Just like the theta and gamma rhythms, also SWR in the hippocampus have shown to be phase-locked to respiration, with a higher probability of SWR occurrence during the early inhalation phase, and the elimination of the effect of respiration upon the inhibition of the OB (Karalis & Sirota, 2022; Liu et al., 2017).

Finally, a fourth rhythm involved in memory processes, potentially related and complementary to SWR, are so called dentate spikes (DS), a short duration (up to 40 ms), large amplitude spikes visible in the dentate gyrus (Bragin, et al., 1995; Headley et al., 2017). Whereas SWR have been found during a variety of behavioral states (Buzsáki, 1986), DS seem to be limited to slow-wave sleep and awake immobility (Bragin, et al., 1995). Furthermore, the two rhythms seem to influence each other's occurrence, with a higher chance of DS occurring immediately after SWR, and a suppressive effect of DS on SWR (Bragin, et al., 1995; Headley et al., 2017). Recent research has implicated DS in specific memory consolidation functions (Lensu et al., 2019; Nokia et al., 2017), and since then, just like SWR, DS have been found to be influenced by respiration, with a higher likelihood of DS occurring after inhalation (Karalis & Sirota, 2022).

Taken together, we have a variety of research showing how respiration can modulate various cortical and hippocampal rhythms underlying memory function (for review, see Heck et al., 2019; Molle & Benoit, 2019; Nokia & Penttonen, 2022). These theoretical ways for respiration to influence memory function are also reflected in behavioral experiments in both mice and humans.

In an intracranial EEG study with humans who were undergoing epilepsy treatment, breathing was found to synchronize electrical activity in various brain regions, including the hippocampus (Zelano et al., 2016). Interestingly, oscillatory power peaked during inhalation and disappeared when the breathing route was switched to mouth breathing instead of nasal breathing. Within the same experiment, but in a separate group of participants not undergoing epilepsy treatment, behavioral performance was investigated in a visual memory task. Images presented during the inhalation phase of respiration were recalled more reliably than those presented in the exhalation phase. This effect was only present when the participants performed the task while breathing through their nose, but not while breathing through their mouth (Zelano et al., 2016). However, Johannknecht and Kayser (2022) were unable to replicate the nasal effect and did not observe any performance difference in visual recognition memory between items encoded during the inhalation phase compared to exhalation.

Similarly, another study found that accuracy and response time were negatively affected in a visual recognition task when the retrieval process occurred during the transition from exhalation to inhalation. However, this result held only true when the stimuli were presented phase-locked with respiration, and not when the stimuli were presented randomly across the breathing cycle, and is therefore harder to interpret (Nakamura et al., 2018). These results were later replicated, again showing significantly slower response time and lower accuracy, when participants were asked to respond during the transition from exhalation to inhalation, compared to other times during the respiratory cycle (Nakamura et al., 2022). Moreover, another study investigating the effects of breathing route on performance in a *n*-back working memory task, did not find a significant difference in accuracy and response time when the task was performed during nose, or mouth breathing (Lee et al., 2019).

Furthermore, studies using a trace eyeblink classical conditioning paradigm to model associative learning, have reported higher conditioning in the group where the conditioning stimuli were presented during exhalation, than in the groups where the stimuli were presented during inhalation, or at random (Waselius et al., 2019, 2022).

It is difficult to establish exactly which phases of respiration are driving the observed effects, as they vary from study to study. Additionally, studies are difficult to compare because they differ in their methodology for measuring respiration and classifying respiration phases. Taken together, the overall findings paint a mixed picture of the effect of breathing on encoding and recognition.

In contrast to studying the effects of breathing on memory encoding and retrieval, Arshamian et al. (2018) investigated the effect of respiration route on the consolidation of olfactory memory. They demonstrated that odors consolidated during nasal breathing were remembered significantly better than those consolidated during mouth breathing (Arshamian et al., 2018).

A study investigating spatial memory in rats found increased coherence of delta, theta, and gamma-band oscillations between the OB and the entorhinal cortex, a brain area associated with working memory, during correct compared to wrong trials in a Y-maze (Salimi et al., 2021). Additionally, low-frequency oscillations in the OB modulated power and phase of gamma oscillations in the entorhinal cortex more strongly, and the influx of information from the OB to the entorhinal cortex was increased at delta and gamma bands. While respiration was not measured per se, the authors hypothesized that the observed OB oscillations were coordinated by nasal respiration (Salimi et al., 2021). Moreover, it has been shown that mechanical ventilation-induced memory impairments could be alleviated in rats by delivering rhythmic air-puffs into the nasal cavity (Ghazvineh et al., 2021). The authors hypothesized that alteration in brain oscillations due to the absence of nasal airflow and OB stimulation during ventilation via tracheotomy, is the cause of the memory impairment often found after mechanical ventilation in humans, and that nasal air puffs could keep up the OB stimulation and thereby prevent the ventilation-induced memory impairment (Ghazvineh et al., 2021).

Overall, the study of respiratory influences on memory function has yielded conflicting and diverse results. This makes it difficult to compare and contrast the findings of various studies. While there is a possibility that breathing can influence memory performance, it is necessary to demonstrate a clear link between breathing and brain activation and subsequent memory performance in humans, and this has not yet been done. Replications with larger sample sizes are necessary before too much confidence can be placed in the specific outcomes of the studies conducted to date. The investigation of cognitive influences of respiration in humans is a new and rapidly developing field. While the progress that is being made is indeed exciting, it remains to be seen which results will withstand the test of time.

3 Research aims

The overall aim of my thesis is to enhance our understanding of how respiration influences pupil size dynamics and visual recognition memory. To achieve this, the thesis is divided into five separate yet complementary studies. In **Study I**, I systematically reviewed the existing knowledge on how respiration affects pupil size dynamics in humans, identifying significant gaps in our understanding and unresolved questions. **Study II** targeted these outstanding questions with new experimental research. **Study III** investigated the effect of respiration on visual recognition memory and its associated neural processing. **Study IV** investigated the effect of respiration on visual recognition memory during rapid serial visual presentation. In **Study V**, I shifted my focus to chemosensory research, which serves as a foundation for contemporary investigations into the effects of respiration on cognition, perception, and behavior. Here, I investigated potential side effects of hormonal contraception on chemosensory perception.

3.1 Respiratory influences on pupil size dynamics

Study I aimed at creating an overview of what is known about respiratory influences on pupil size dynamics in humans by performing a systematic literature review.

Study II aimed at answering critical outstanding questions revealed by **Study I**, particularly studying the potential effects of breathing phase and breathing route on pupil size.

3.2 Respiratory influences on visual recognition memory

Study III aimed at determining the effect of breathing phase and breathing route on performance in a visual recognition memory task and the underlying brain activity, by presenting stimuli phase-locked to either the inhalation or exhalation onset.

Study IV aimed at building upon the results of study III, by investigating respiratory effects on visual recognition memory in scenarios involving rapid serial visual presentation, a considerably larger sample size, and a built-in replication.

3.3 Hormonal contraceptives and chemosensory perception

Study V aimed at investigating potential side effects of hormonal contraceptives on chemosensory perception.

4 Materials and methods

4.1 Systematic literature review

In **Study I**, we set out to gain an overview of the literature about respiratory influences on pupil size dynamics in humans. To do so in a thorough and systematic manner, we followed several formal steps.

The overall process of conducting the systematic review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The PRISMA guidelines consist of a 27-item checklist to aid the authors in being transparent, complete, and accurate in their literature assessment (Page et al., 2021).

Together with university librarians, a systematic search of the scientific literature databases MEDLINE, Web of Science, and PsycInfo, was performed with relevant search terms. Following the screening of all the articles returned by the systematic search, and the identification of a subset of relevant articles, we proceeded to synthesize the results by grouping the articles by the breathing parameters they addressed (breathing phase, depth, rate, and route). In the next step, we assessed the quality of the included articles using QualSyst, a tool developed to evaluate the internal validity of quantitative studies of various methodologies, consisting of 14 questions which you answer for each included article (Kmet et al., 2004). After summarizing the results of all the studies for each breathing parameter, and the evaluation of the quality of the individual articles, we proceeded with assessing the strength of the evidence available for each of the breathing parameters to influence pupil size dynamics. This assessment was conducted in line with the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach (Guyatt et al., 2008). Based on the GRADE method, a body of evidence can receive one of four scores: High, moderate, low, or very low, which summarize the grader's confidence in the body of evidence. Besides the GRADE scoring, we also wanted to give a visual representation of the strength of each body of evidence. To do so, we developed a five-dimensional graph for the individual articles that belonged to each body of evidence, which showed the characteristics of each individual study along the dimensions of: sample size, QualSyst score, whether the article presented evidence for an effect or not, whether the main aim of the study was to investigate respiratory effects on pupil size dynamics, and what kind of statistics the study employed.

To enhance objectivity throughout the research process, each step, from article screening to evidence grading, was independently conducted by at least two authors. After each step, we compared our assessments and solved inconsistencies among raters through discussion. This collaborative approach ensured a comprehensive and unbiased evaluation of the available evidence.

4.2 Research participants

All participants included in this thesis were in good health and provided written informed consent before participating in any of the studies. Furthermore, for all the studies investigating respiration (**Studies II-IV**), participants were required to be able to breathe freely through the nose (and for **Studies II** and **III** also through the mouth), have normal vision or corrected-to-normal vision with contact lenses, and have a normal sense of smell.

Study II included 50 participants (37 females), ranging in age from 18 to 42 years (mean = 28.2 years). All participants were compensated for their participation with movie ticket vouchers. For the analysis, 10 participants had to be excluded because they did not return for their second recording session (n = 2), or the quality of their pupil size recordings was insufficient (n = 8).

Study III included 25 participants (16 females), ranging in age from 20 to 33 years (mean = 26.7 years). All participants were compensated for their participation with movie ticket vouchers. Two participants had to be excluded because they did not comply with the instructions or withdrew from the study. An additional three participants had to be excluded from the electrophysiological data analysis because the data was of poor quality.

Study IV included 93 participants in the first experiment, of which 21 had to be excluded due to difficulties breathing through their nose (n = 5), misunderstanding the task (n = 2), or poor electro-oculogram signal quality resulting in poor blink identification (n = 14). This resulted in 72 participants (42 females), ranging in age from 18 to 43 years (mean = 28.3 years) left for data analysis. An additional 168 participants were recruited for the second experiment, of which 26 had to be excluded due to low performance (n = 18), poor electro-oculogram quality (n = 7), or because they aborted the experiment (n = 1). This resulted in 142 participants (104 females), ranging in age from 18 to 54 years (mean = 27 years) being included in the analysis. All participants were compensated for their participation with movie ticket vouchers.

Study V included 60 women, ranging in age from 18 to 35 years (mean = 25 years). Twenty-six of the participants were using monophasic or biphasic oral hormonal contraceptives, whereas the other 34 women had a naturally regulated menstrual cycle of normal range (26–33 days). The participants were compensated with 60$.

4.3 Breathing measurements

Throughout **Studies II** – **IV**, we measured respiration from our participants, and over the course of the studies our methods have changed and evolved as we learned which setups were more comfortable for our participants, and what led to more reliable data.

For **Study II** we used a non-restrictive breathing mask that was attached to a breathing cannula to obtain a direct measure of airflow (0202-1199, Tiga-Med, Germany), as well as attaching a temperature probe (MLT415/D, ADInstruments, Colorado, US) to the inside of the mask. The temperature probe detects changes in temperature as participants in- and exhale. As we exhale

warm air, exhalation is detected as an increase in temperature, and inhalation is detected as a decrease in temperature. Both airflow induced pressure changes and breathing-dependent changes in temperature have been validated as sensitive and reliable breathing measures (Johnson et al., 2006). Using two temperature measures assures higher fidelity of the data quality, and while the airflow measurements seem to be slightly more time sensitive, the temperature measurements proved to be less noisy and were the ones that ended up being used for further data analysis. As we measured nose and mouth breathing in turns, the breathing route that was not being measured was covered with surgical tape to prevent the participants from accidentally breathing through the wrong breathing route.

For **Study III** we used a dual port silicone rubber face mask (Model 7940, Hans Rudolph, Inc., Shawnee, USA) to facilitate the measurement of separate breathing routes. A small temperature probe (same as for **Study II**) was inserted into the port of the breathing route that was being used, whereas the other port was blocked, preventing the use of the wrong breathing route.

For **Study IV** we only measured nose breathing by recording nasal airflow using a birhinal nasal cannula connected to a spirometer pod (30 Hz low-pass filter) that measures pressure changes via a differential pressure transducer (response time ~0.5 ms).

For all studies, all breathing signals were amplified, digitized at 1000 Hz (LabChart 7.0, ADInstruments, Colorado, US), and low-pass filtered at 5 Hz (PowerLab 16/35, ADInstruments, Colorado, US).

4.4 Pupil size measurements

Measuring pupil size and reactivity is a common tool in psychological research. While pupils constrict in response to light and near fixation, psychologists have mostly been interested in how the pupil responds to cognitive activity, such as its dilation in response to increased levels of arousal or mental effort (Mathot, 2018).

For **Study II** pupil size was measured at rest under constant lighting conditions. We made use of a Gazepoint GP3 eyetracker which films the eyes with a sampling rate of 60 Hz and recorded with the Gazepoint software. These recordings provided us with a continuous signal, indicating how pupil size changed over time in units of pixels and mm. Furthermore, the pupil data was preprocessed in several steps to interpolate blinks and identify invalid data. The preprocessing generally followed the suggestions by (Mathôt & Vilotijević, 2022). To be able to compare pupil size values across participants, and to make any changes in pupil size easier to interpret, we converted pupil size values to z-scores for each participant.

4.5 Electroencephalography (EEG)

4.5.1 Underlying source of the EEG signal

Electroencephalography is a noninvasive brain imaging method based on recording the electrical activity produced by the neurons in the brain as they communicate with each other. Neurons at rest have a stable membrane potential of approximately -70 mV at the axon hillock, which is actively maintained by regulating the concentration of sodium, chloride, and potassium ions, inside and outside the cell. The stable membrane potential can be changed by voltage changes transmitted from other neurons, or by neurotransmitters that interfere with the balancing of ion concentrations inside and outside the cell. If the neuron is depolarized to a certain threshold, typically around -55 mV, a pulse of about 100 mV in amplitude, called an action potential, is created and travels along the axon and triggers a postsynaptic potential in the next neuron. A stronger stimulus leads to more frequent, rather than stronger action potentials, and if the total amount of excitation from postsynaptic potentials exceeds the threshold potential, it triggers an action potential in the next neuron. If enough neurons that are aligned in the same direction fire simultaneously, the change in electrical activity can be detected from electrodes attached to the scalp. Although action potentials have an amplitude approximately ten times higher than postsynaptic potentials, the postsynaptic potentials have a much longer duration (~5-100 times longer), and therefore postsynaptic potentials are considered to be the main generators of the EEG signal. The postsynaptic potentials from a large group of neurons are called local field potentials.

4.5.2 Event-related potentials (ERPs)

Besides spontaneous brain activity, we can also detect how the brain responds to specific stimuli, by looking at the changes in brain activity time-locked to a specific stimulus. Characteristic brain responses to specific stimuli have been called event-related potentials. These event-related potentials are typically characterized by the peak latencies and amplitudes of the main deflections and the brain areas over which they are recorded. Event-related potentials are generally quite small compared to ongoing spontaneous brain activity, and therefore, they can only be detected by averaging the signal of many trials.

For **Study III** we recorded EEG to investigate whether two well-known event-related potentials underlying recognition memory, are affected by breathing. Specifically, we looked at the FN400 component which consists of a negative voltage deflection occurring around 300 to 500 ms post stimulus onset, recorded from a set of electrodes covering the frontal part of the brain. The FN400 component is thought to be triggered by, and an indicator of, familiarity-based recognition (Rugg & Curran, 2007). Furthermore, we looked at the late parietal effect (LPE), a positive voltage deflection occurring around 400 to 800 ms post stimulus onset, recorded from a set of electrodes covering the parietal part of the brain. The LPE component is thought to correlate with recollection-related processes of memory (Rugg & Curran, 2007).

4.6 Episodic memory tasks

In **Studies III** and **IV** we made use of two different types of visual memory tasks to investigate how breathing shapes episodic visual recognition memory performance.

4.6.1 Visual recognition memory task

In **Study III** we employed a visual recognition memory paradigm. During encoding we presented the participants with a series of 60 images, each image was presented for one second, starting either during inhalation onset or exhalation onset (see Figure 4.1A). After this, the participants had a five-minute break. Next during recognition trials, the 60 images were presented to the participants again, but interspersed with 60 new images that functioned as lures (see Figure 4.1B). Again, the images were presented in random order for one second each, either during the onset of inhalation or exhalation, and the participants had to answer whether or not they had seen the image before during encoding.

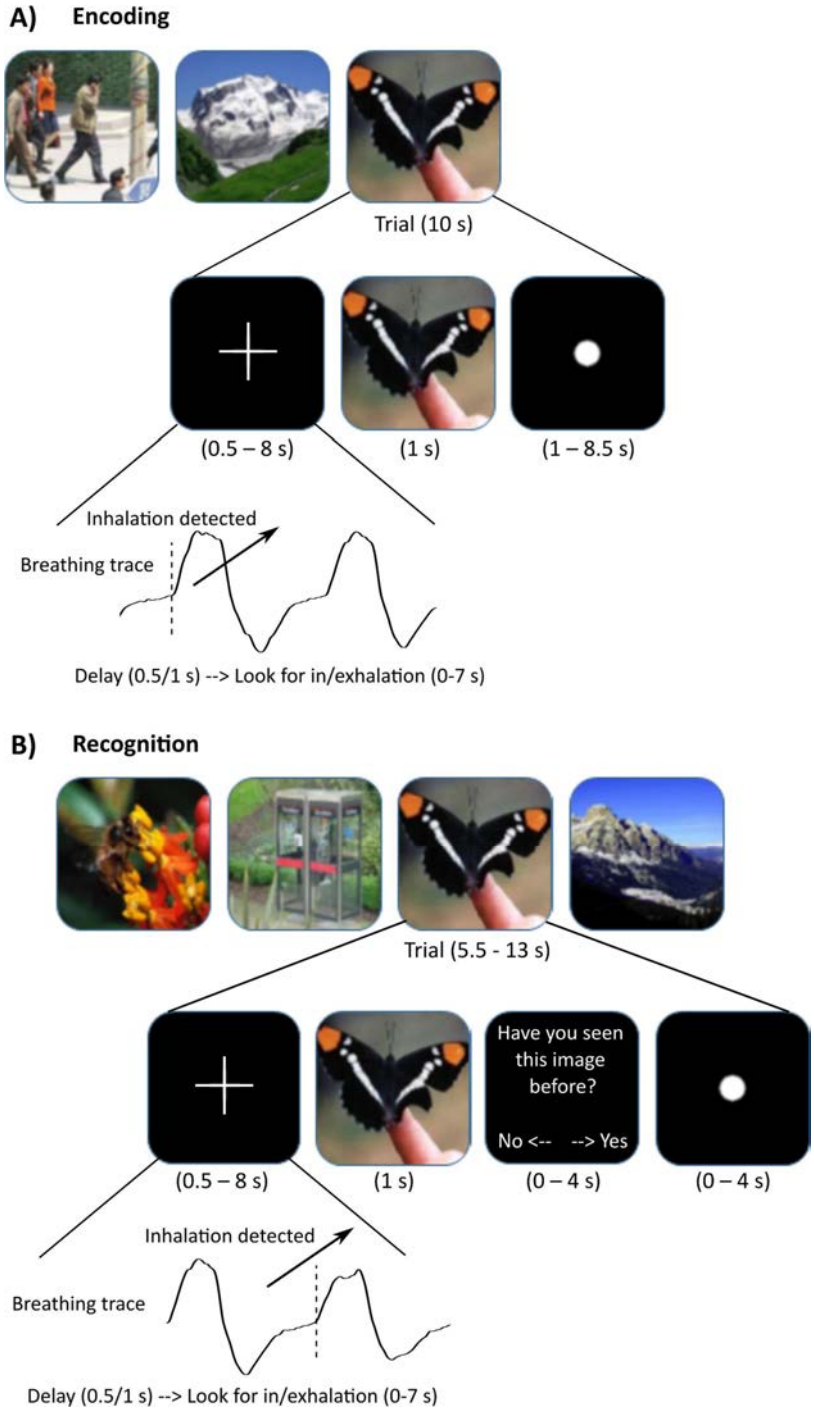

Figure 4.1. Study III paradigm overview. A) The encoding blocks consisted of 60 trials lasting 10 s each. Each trial consisted of a delay period of 0.5 or 1 s, followed by a period of up to 7 s where the breathing data was scanned to detect an inhalation or exhalation onset. Upon detecting the phase onset, an image was presented for 1 s, followed by the presentation of a fixation dot for 9 s minus the

duration of the fixation cross presentation. **B)** The recognition blocks consisted of 120 trials lasting between 5.5 to 13 s each. Each trial consisted of a delay period of 0.5 or 1 s, followed by a period of up to 7 s where the breathing data was scanned to detect an inhalation or exhalation onset. Once the phase onset was detected, an image was presented for 1 s, followed by the question-and-answer segment for up to 4 seconds, followed by the presentation of a fixation dot for 4 s minus the time spent to complete the previous segment.

Memory performance in **Study III** was quantified by *d*-prime (*d'*), a commonly used sensitivity index used to measure the ability to discriminate between targets and lures, where a score of 0 indicates at chance performance, and higher scores indicate increasingly better performance (see Figure 4.2; Macmillan & Creelman, 2005). D-prime was calculated using the following formula:

$$d' = z(\text{Hit rate}) - z(\text{False Alarm rate})$$

We also calculated the response criterion (*c*), which indicates the degree of strength that has to be exceeded for an item to be accepted as previously experienced using the following formula:

$$c = -\frac{z(\text{Hit rate}) + z(\text{False Alarm rate})}{2}$$

The response criterion c is a unit measuring the level of preference for answering "old" or "new". Negative values indicate a liberal response bias with a tendency to respond old, positive values indicate a conservative response bias with a tendency to respond new, and zero indicates a neutral, unbiased, and optimal response strategy (see Figure 4.2).

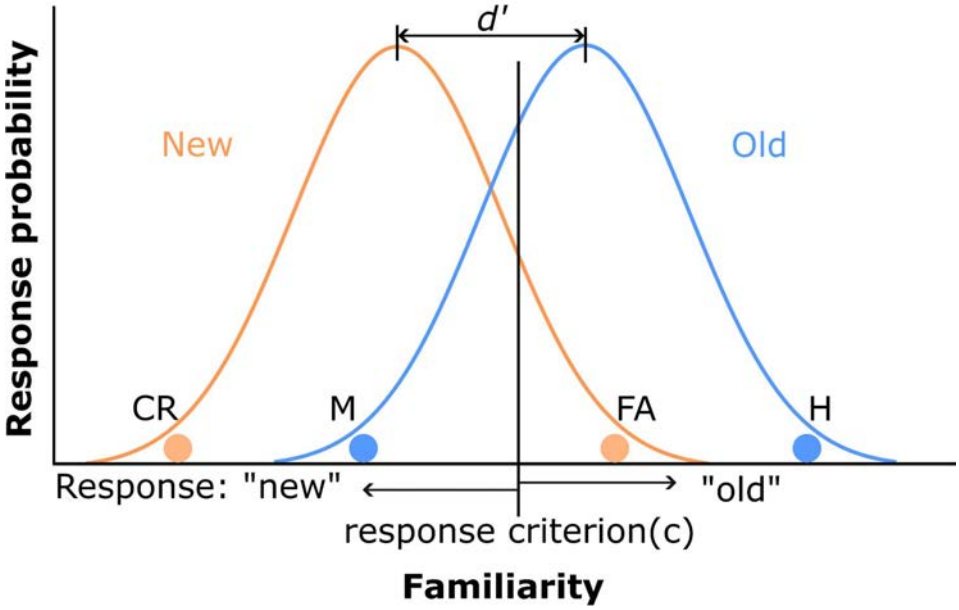

Figure 4.2. Signal detection theory. Participants decide whether the image presented to them is new or old. They make their decision based on how familiar the image is to them, and on their response bias as indicated by the criterion (c). The greater the *d'* score, the better the participant is at discrimination between old and new images. The higher the c score, the greater the likelihood that the participant classifies the image as new, independent of its familiarity. The opposite is true for negative c scores. CR = correct rejection, M = miss, FA = false alarm, H = hit.

4.6.2 Rapid serial visual presentation (RSVP) task

In **Study IV** we made use of a rapid serial visual presentation (RSVP) repetition paradigm. This paradigm has been validated (Thunell & Thorpe, 2019a, 2019b), and relies on several aspects of basic visual processing and memory. The paradigm was therefore thought to be a good candidate for investigating potential effects of breathing phase on task performance. During the experiment, participants were shown RSVP streams of natural images presented at a rate of 12 images per second. Each RSVP stream contained approximately 564 images and lasted 47 seconds. Moreover, each RSVP stream contained 12 "repetition sequences" which consisted of an image appearing five times with one non-repeating image in between each repetition. The repetition sequences were separated from each other in time by 2.5-3.5 seconds of non-repeating images. Each participant was presented with 20 RSVP streams during the experiment, and at the end of each RSVP stream the participants had to identify all of the 12 repeated images in a sequential two-alternative forced choice memory task. The repeated images were presented in random order that was different from their order of appearance in the RSVP stream, together with a lure that consisted of a non-repeated image from the RSVP stream (see Figure 4.3).

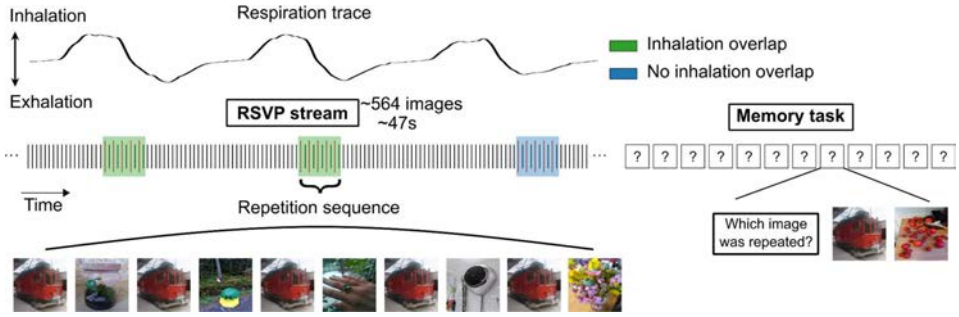

Figure 4.3. RSVP paradigm. A part of a RSVP image stream is shown; each vertical line depicts an image presentation. At random time points, an image (here, the red tram) was presented five times in a "repetition sequence" with one non-repeating image in between each repetition. In the Memory task that followed each image stream, the 12 repeated images had to be identified in a two-alternative forced choice task where the lures were non-repeated images from the same stream.

4.7 Chemosensory testing

For **Study V** we employed a series of chemosensory tasks, to assess the chemosensory sensitivity and perception among women taking oral hormonal contraceptives, and a freely cycling control group.

We assessed olfactory function by testing odor detection threshold, quality discrimination, and cued identification.

4.7.1 Odor detection threshold

For the odor detection threshold task participants were blindfolded and then presented with three bottles, one of which contained a diluted odor (n-butanol or peanut oil), and the other two contained only the odor-less solvent (1,2 propanediol or silica-filtered, light mineral oil), and the participant had to indicate which of the bottles contained the odor. Two odors (n-butanol and peanut oil), were chosen for their different chemical composition (monomolecular, complex mixture, respectively) and ecological relevance ("chemical odor", food-associated odor, respectively). The odors were diluted to 16 different concentrations, and each subject started with the weakest odor concentration and worked their way up the concentration ladder until they successfully identified the stimuli in two successive trials, upon which the staircase was reversed, and the odorant concentrations were lowered again. Seven staircase reversals were collected and the mean of the last four reversals served as the threshold estimate.

4.7.2 Odor quality discrimination

We used the Sniffin' Stick odor discrimination test developed by Hummel and colleagues to assess participants' odor quality discrimination ability (Hummel et al., 1997). This test consists of presenting participants with triplets of felt-tipped odorized pens, two of which contain the

same odor, and the third pen contains a different odor. The participants have to pick out which of the pens contains the different odor in a series of 16 triplets.

4.7.3 Cued odor identification

The Monell Extended Sniffin' Sticks Identification Test (MONEX-40) was used to assess odor identification ability among the participants (Freiherr et al., 2012; Hummel et al., 1997). The test consists of a set of 40 felt-tipped odorized pens, each of which contained a different odor. The participants were tasked with identifying the odor presented to them out of a four-choice alternative.

4.7.4 Taste detection threshold

To assess taste sensitivity, we used the tastants quinine monohydrochloride dehydrate and sucrose. These two compounds were chosen to cover bitter, and sweet sensitivity (i.e., toxic and nutrition signals, respectively). Both tastants were diluted in Millipore-filtered deionized water to 18 different concentrations. To exclude potential olfactory information from the decision-making process, participants wore noseclips during the taste detection task. Two cups were presented to the participants in each trial. One cup contained 10 ml of the tastant solution, whereas the other cup was filled with the clean diluent in equal amount. On each trial, the participant poured the entire content of a cup into their mouth, gently swirled it around for 10 seconds, and then spat it out and rinsed with deionized water before proceeding with the content of the second cup. Participants then selected which cup contained the tastant. Each subject started with the middle tastant concentration and worked their way up the concentration ladder until they successfully identified the stimuli in two successive trials, upon which the staircase was reversed and the tastant concentrations were lowered again. Five staircase reversals were collected, and the mean of the last four reversals served as the threshold estimate.

4.7.5 Taste perception

Participants further rated the tastants for perceived pleasantness, familiarity, intensity, and quality. Pleasantness and familiarity were rated on a visual analogue scale ranging from "extremely unfamiliar/unpleasant" to "extremely familiar/pleasant," with "neutral" in the middle. Intensity and quality were rated on a labelled magnitude scale ranging from "no sensation" to "strongest imaginable," with the steps "barely detectable," "weak," "moderate," "strong," and "very strong" in between. Different scales were used because the more cognitive perceptions of familiarity and pleasantness tend to scale linearly, whereas intensity and quality have a close link to physical stimuli and therefore scale logarithmically (Green et al., 1996).

4.7.6 Trigeminal detection threshold

Trigeminal sensitivity was assessed using a nasal lateralization task in which participants were presented with clean air into one nostril and odorized air into the other nostril simultaneously, after which they indicated which nostril received odorized air. This task works because humans can only lateralize chemical vapor when concentrations reach high enough levels to elicit a trigeminal sensation (Kobal et al., 1989; Wysocki et al., 1997). The odor chosen for this task

was menthol because it has a clear trigeminal component. L-menthol crystals were dissolved in 1,2 propanediol and diluted to 16 different concentrations. Each subject started with the weakest l-menthol concentration and worked their way up the concentration ladder until they successfully identified the stimuli in two successive trials, upon which the staircase was reversed, and the l-menthol concentrations were lowered again. Seven staircase reversals were collected, and the mean of the last four reversals served as the threshold estimate.

4.8 Statistical methods

4.8.1 Permutation tests

In **Study II**, we used permutation tests, a non-parametric method that only relies on the assumption of exchangeability. To test the null hypothesis that pupil size does not vary over the course of the breathing cycle, we generated a null distribution by calculating the mean of random pupil size samples from all across the breathing cycle 10,000 times. We then compared this distribution with the mean value of all the pupil size samples taken from a specific part of the breathing cycle, and calculated a *p*-value by computing how extreme our observed mean is in relation to our generated null distribution.

4.8.2 Bayesian statistics

For **Studies III** to **V**, we made use of Bayesian statistics instead of, or complementing traditional *p*-value null hypothesis statistical testing. Statistical inference based on Bayesian methods has various advantages over *p*-value null hypothesis statistical testing (for review, see Wagenmakers et al., 2018). One of these advantages is that the Bayes factor quantifies the evidence that data provide for the null hypothesis (H_0) vs the alternative hypothesis (H_1), and that it can actually quantify evidence in favor of H_0.

While *p*-values are calculated conditional on H_0 being true and quantify how probable data at least as extreme as your observed data, are under H_0, it does not tell you anything about how likely your data is under H_1. The Bayes factor on the other hand, compares how much the data provides support for H_0 against H_1. This is more intuitive and allows not just the rejection of H_0, but also the quantification of evidence for H_0. Quantifying the evidence for H_0 makes it possible to distinguish between evidence of absence and absence of evidence (Dienes, 2014), which is a very important distinction.

As most researchers are still more familiar with *p*-values, than with Bayes factors, for **Studies III** and **IV**, we still reported *p*-values alongside Bayes factors, to make it easier for the readers to interpret our findings and also to see how the two statistical measures compare.

4.9 Ethical considerations

Studies II to **V** were done with the help of human volunteers; as such it is important to consider what ethical considerations are at play to ensure that no harm is done. Three main steps were taken in every study before collection of any data began. First of all, we sat down and thought through every step of the study with the purpose of identifying any possibility of harm for our volunteers. Second, we wrote out a detailed plan for our study and our ethical considerations and sent this to the local ethical review board for consideration, ensuring a second opinion. Thirdly, all participants in our studies received details about the study they were participating in, in advance to give them time to think through whether they truly wanted to participate in our studies. All participants provided written informed consent on the day of the experiment and were encouraged to ask questions if they had any. They were also informed that they could abort the experiment at any time, without needing to provide an explanation, and without any loss of compensation.

4.9.1 Personal data

For all studies in this thesis that included human participants, personal information such as name, sex, age, and sometimes contact information was collected. Furthermore, various physiological measures were recorded, and in the case of **Study V**, even medical information. To ensure such sensitive data does not fall into the wrong hands, and to avoid the possibility of individual identification, all data was stored in anonymized form on a server with restricted access. Furthermore, for all studies, data were only presented on a group-level or in a manner that made it impossible to attribute the data to a specific individual.

4.9.2 Testing during a pandemic

A large part of my time as a PhD student overlapped with the Covid-19 pandemic. Although our understanding of Covid-19 was very limited at the beginning of the outbreak, it was clearly a respiratory disease that was highly infectious. This meant not only that close contact with other people such as in a lab environment was heavily discouraged, but particularly experiments that required the measuring of respiration, and putting equipment into close contact with participants' respiratory orifices felt ethically unacceptable. Therefore, we cancelled one study completely, and postponed data collection for another study when the second wave of Covid-19 hit. Furthermore, when we did go back to testing participants in the lab, we added additional safety measures such as demanding that all participants washed their hands upon arrival, the wearing of a facial mask by the experimenter, use of one-time-use equipment wherever possible, and additional cleaning and disinfection routines of the surfaces and equipment that were being reused.

5 Results

In the following section I will briefly summarize the main findings for each of our studies. For a detailed overview, the reader is referred to the full-length studies amended at the end of this thesis as separate appendices.

5.1 Study I: A systematic literature review of respiratory influences on pupil size dynamics

Respiratory influences on the pupil light reflex have been reported more than 50 years ago (Golenhofen & Petrányi, 1967). Since then, systematic fluctuations over the course of the breathing cycle have been described (Borgdorff, 1975), and the notion that inhalation is accompanied by pupil dilation, and exhalation by pupil constriction has become the general understanding in the field (Ashhad et al., 2022). Because both breathing and pupil size are regarded as important measures when studying the brain and behavior, we set out to synthesize the progress that has been made since the first respiratory influences on pupil size were reported.

The initial literature search returned 1,529 records, from which we identified 31 relevant studies and reports. We categorized the relevant studies according to which of the following breathing parameters they reported; breathing phase, depth, rate, or route. Furthermore, we classified the studies with regard to what kind of task/stimuli they used, and whether an interaction between breathing and pupil measures was a main study outcome.

We found six studies that looked at breathing phase, six studies that looked at breathing depth, 20 studies that looked at breathing rate, and no studies that looked at breathing route and therefore this parameter could not be included. For each of the breathing parameters, we assessed the strength of the body of evidence that the relevant studies provided for that particular breathing parameter influencing pupil size dynamics. Because there were so many studies that included breathing rate as a measure, we divided that group into the articles that directly set out to assess an influence of breathing rate on pupil size dynamics, and those that included the breathing rate as a measure, but did not have it as a main study outcome.

Overall, we found only low to very low evidence that any of the breathing parameters that were studied affect pupil size dynamics in humans (see Table 5.1 for a summary of the GRADE assessment). The reason for this is that many of the reviewed studies suffered from small sample sizes, methodological and statistical shortcomings, as well as a huge diversity in methods. Taken together, this demonstrates that the relatively straight-forward question of whether breathing affects pupil size dynamics has not yet been conclusively answered.

Breathing parameter	Study design	Risk of Bias	Inconsistency of results	Indirectness of evidence	Imprecision (uncertainty of results)	Total sample size across all studies	GRADE
Phase	Moderate	OK	OK	OK	↓	84 (6)	Low
Depth	Moderate	OK	↓	↓	↓	145 (6)	Very Low
Rate direct	Moderate	OK	↓	OK	↓	188 (8)	Very Low
Rate indirect	Moderate	OK	↓	↓	↓	368 (12)	Very Low

Table 5.1. Certainty of evidence as assessed by GRADE. The columns represent the categories given in the GRADE handbook and the arrows represent up- or downgrading (Guyatt et al., 2008). Assessment of study design took account of the study's quality assessment score. Risk of bias mainly evaluated confounding factors and how measurements were taken. The inconsistency category dealt with the incoherence in results between studies, and indirectness with whether the pupil and breathing interaction was the main study outcome. Imprecision dealt with sample size and application of statistical methods. Instead of assessing publication bias we show the total number of participants and number of studies for each study outcome in the seventh column. The GRADE column shows the final GRADE score for the evidence of each study outcome.

5.2 Study II: An empirical study of respiratory influences on pupil size dynamics

Following the somewhat surprising discovery that the evidence for respiratory influences on pupil size dynamics in humans is actually quite weak, and that the interplay between breathing and pupil size is not well understood, we set out to directly address the outstanding questions that we identified in **Study I**. More specifically, we studied the effects of respiration on pupil size dynamics over time, breathing route, breathing phase, and breathing frequency in humans at rest (i.e., without interference from a task).

We did not observe any changes in averaged pupil size across time when we plotted pupil size around inhalation and exhalation over six second time windows. When we instead plotted pupil size across the breathing cycle, we found small but systematic differences, with pupil size peaking around exhalation onset, and being at its smallest around inhalation onset (see Figure 5.1). This is in direct contrast to the current understanding that pupil size increases during inhalation. In addition, we found that the strength of the correlation between the breathing and the pupil signal was strongly negatively correlated with the breathing frequency; the slower the breathing signal, the stronger its correlation with pupil size. As this held true even when calculating the correlation between the breathing signal of one participant and the pupil signal of another participant, we believe that this correlation is largely spurious and caused by the sinusoidal nature of the breathing signal. To test whether there was any correlation and phase synchronization between the breathing signal and the pupil signal, we employed a permutation testing approach where we compared the correlation and phase synchronization degree within subjects, to that between subjects. This showed that within subject correlations and phase synchronizations between breathing and pupil size were slightly, but significantly larger than those between subjects ($p < .001$; see Figure 5.2). Finally, although we did not always statistically compare the results from nose and mouth breathing, they showed very similar patterns of results.

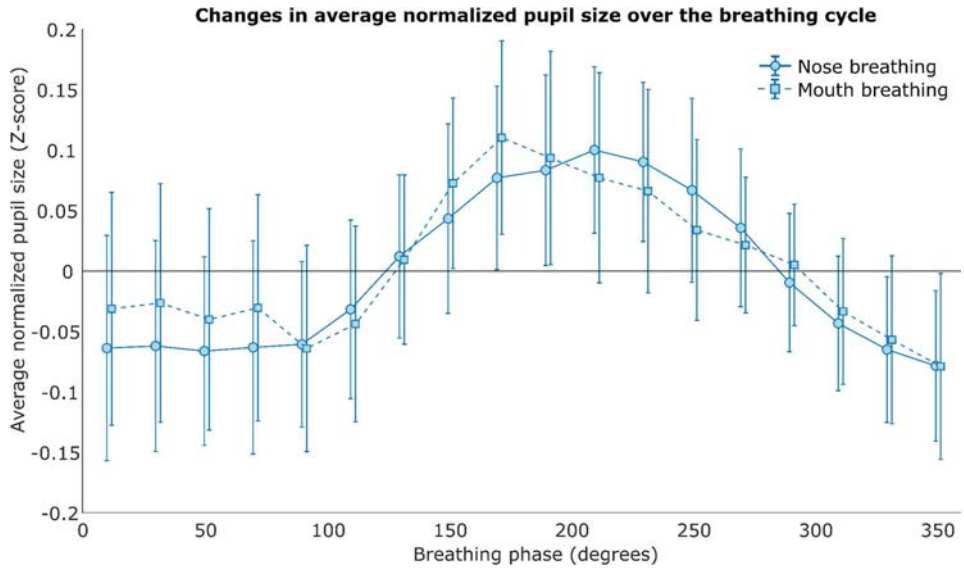

Figure 5.1. Mean normalized pupil size across the breathing cycle. The x-axis depicts the breathing phase in degrees, with zero being the start of inhalation and 180 the start of exhalation. The solid line with circles represents nose breathing, and the dotted line with squares represents mouth breathing. Error bars show the 95% confidence intervals.

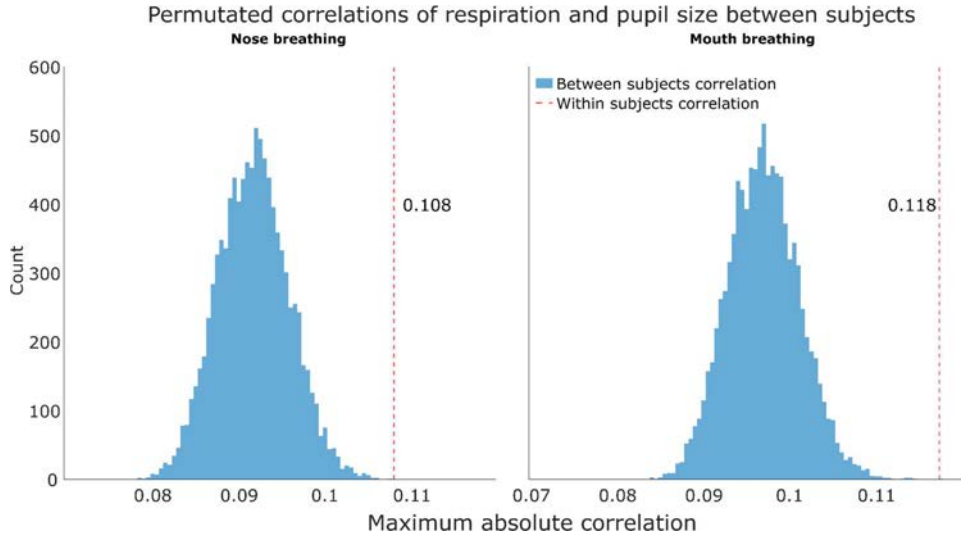

Figure 5.2. Histogram depicting maximum absolute correlations acquired by calculating the mean of the correlations between the breathing signal of each participant and the pupil size signal of a random other subject, compared to the mean correlation found within subjects.

Taken together, we show that pupil size does not increase during inhalation as previously believed. Specifically, we show a small but consistent effect of breathing phase on pupil size, with larger pupil sizes around exhalation onset and smaller pupil sizes around inhalation onset. Furthermore, we show that a spurious correlation between the breathing signal and pupil size exists, that is largely, but not exclusively, driven by breathing rate. And finally, we did not demonstrate changes in pupil size across time or any differences between nose and mouth breathing on pupil size dynamics. The small effects and the confounder of breathing rate might be part of the reason why previous studies investigating respiratory influences on pupil size vary so much in their outcomes and have not been conclusive.

5.3 Studies III & IV: Investigating the effect of breathing on episodic visual memory

Recent studies have suggested that breathing entrains neural oscillations involved in episodic memory processes, thereby potentially influencing memory performance (Fontanini & Bower, 2006; Heck et al., 2019; Herrero et al., 2018; Kay, 2014; Chi et al., 2016; Zelano et al., 2016). Several behavioral studies have tried to assess whether breathing phase affects performance in visual memory tasks, with some reporting increased performance during nasal inhalation (Zelano et al., 2016). However, the results are not that clear, as other studies did not find this effect (Johannknecht & Kayser, 2022). Therefore, we set out to contribute to the question of whether breathing affects visual memory performance with two separate but complementary studies.

In **Study III**, we employed a within-subjects design and a visual recognition memory (VRM) task based on previous studies, in combination with electroencephalography recordings, to investigate the effect of breathing phase and route on VRM and its underlying brain activity. More specifically, we presented images to our participants, phase-locked to either inhalation or exhalation onset during nose and mouth breathing and compared their recognition performance later on across breathing phase and route. Besides their memory performance, we also investigated whether breathing phase or breathing route affected FN400 or LPE, two ERP components related to episodic VRM (Rugg & Curran, 2007).

Our results showed that neither breathing route ($BF_{excl} = 2.0$), nor breathing phase ($BF_{excl} = 4.9$) affected memory performance as measured by *d'* (see Figure 5.3). However, we did detect a slight shift in response bias with participants answering more conservatively during exhalation as compared to inhalation as measured by criterion ($BF_{excl} = 0.4$, $p = .004$). Furthermore, we found a significant effect of breathing route ($BF_{excl} = 0.3$, $p = .037$), and breathing phase ($BF_{excl} = 0.06$, $p = .001$) on the LPE amplitude during encoding (see Figure 5.4). Otherwise, the FN400 and LPE component amplitudes were not, or inconclusively affected by breathing route and phase during encoding or recognition.

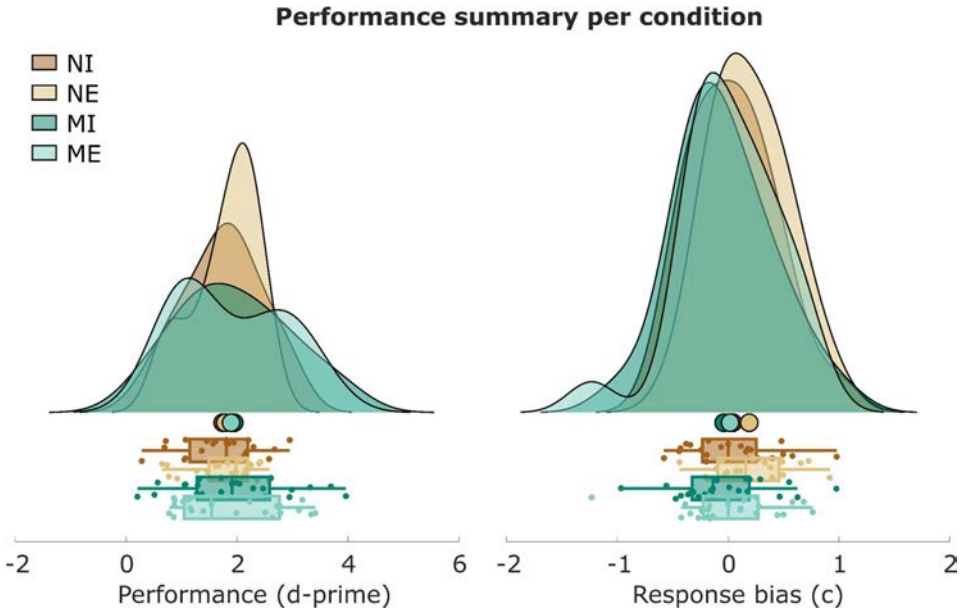

Figure 5.3. Raincloud plot depicting the density and spread of the *d*-prime performance and response bias across subjects and conditions. Small dots show data of individual participants, and large dots show the averaged values per condition. NI = nose inhalation, NE = nose exhalation, MI = mouth inhalation, ME = mouth exhalation.

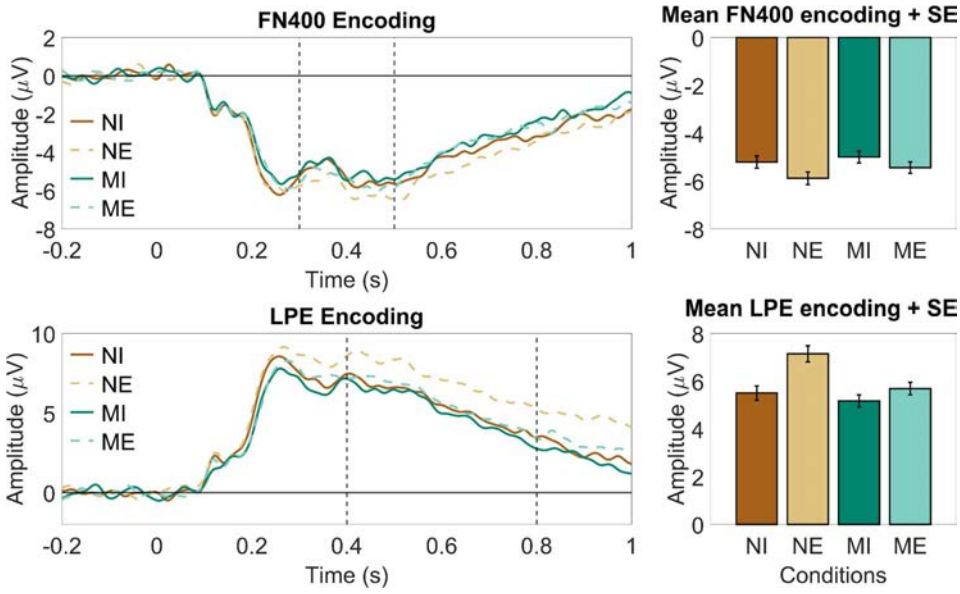

Figure 5.4. FN400 and LPE components during encoding. The vertical dotted lines on the line graph indicate the time period of interest for the FN400 and LPE components. NI = nose inhalation, NE = nose exhalation, MI = mouth inhalation, ME = mouth exhalation.

Thereby, this study provided the first evidence that VRM performance is not affected by breathing route or phase when stimuli presentation is phase-locked to in/exhalation onset. At the same time, like previous studies, we show that certain brain activity patterns that are implicated in memory processes are affected by breathing route and phase.

In **Study IV** we wanted to further investigate potential influences of breathing phase on visual recognition memory. This time we used a different memory paradigm, did not present stimuli phase-locked to any particular part of the breathing cycle, and employed a much larger sample size. The memory paradigm we used consisted of repeated images presented in a rapid serial visual presentation (RSVP) task (Thunell & Thorpe, 2019a, 2019b). We consider this RSVP task to be ideal for studying the effects of respiratory-entrained oscillations on visual memory, because it engages critical aspects of sensory encoding that depend on oscillatory activity, such as fast processing of natural images, repetition detection, memory encoding, and retrieval. Based on previous studies, we hypothesized that repetition detection might be more accurate when the stimuli presentation overlapped with the inhalation phase of the breathing cycle, compared to when there was no overlap.

After classifying the trials as either containing inhalation overlap (46%) or no inhalation overlap (54%), we found no difference in performance across the two conditions ($t(71) = 0.21$, $p = .83$, $d = 0.02$).

To investigate the possibility of a delayed effect of nasal inhalation on cognition, we performed an exploratory lag analysis where we considered delayed effects up to 2.5 seconds with increments of 50 ms. We found significantly (p's $< .05$) better performance for *Inhalation overlap* than *No inhalation overlap* for repeated images presented at a lag of 850 to 1450 ms (gray shading in Figure 5.5A). A complementary Bayesian analysis, however, provided inconclusive Bayes factors for the lags between 850 to 1450 ms.

To follow up on these exploratory findings, we pre-registered a replication study with a larger sample size to see whether these results would replicate.

In Experiment 2, there was again no difference in performance between the images presented during *Inhalation overlap* and *No inhalation overlap.* Furthermore, the exploratory results obtained in Experiment 1 could not be replicated (see Figure 5.5B). This shows the importance of replication studies, but also the necessity for high statistical power and pre-registered protocols.

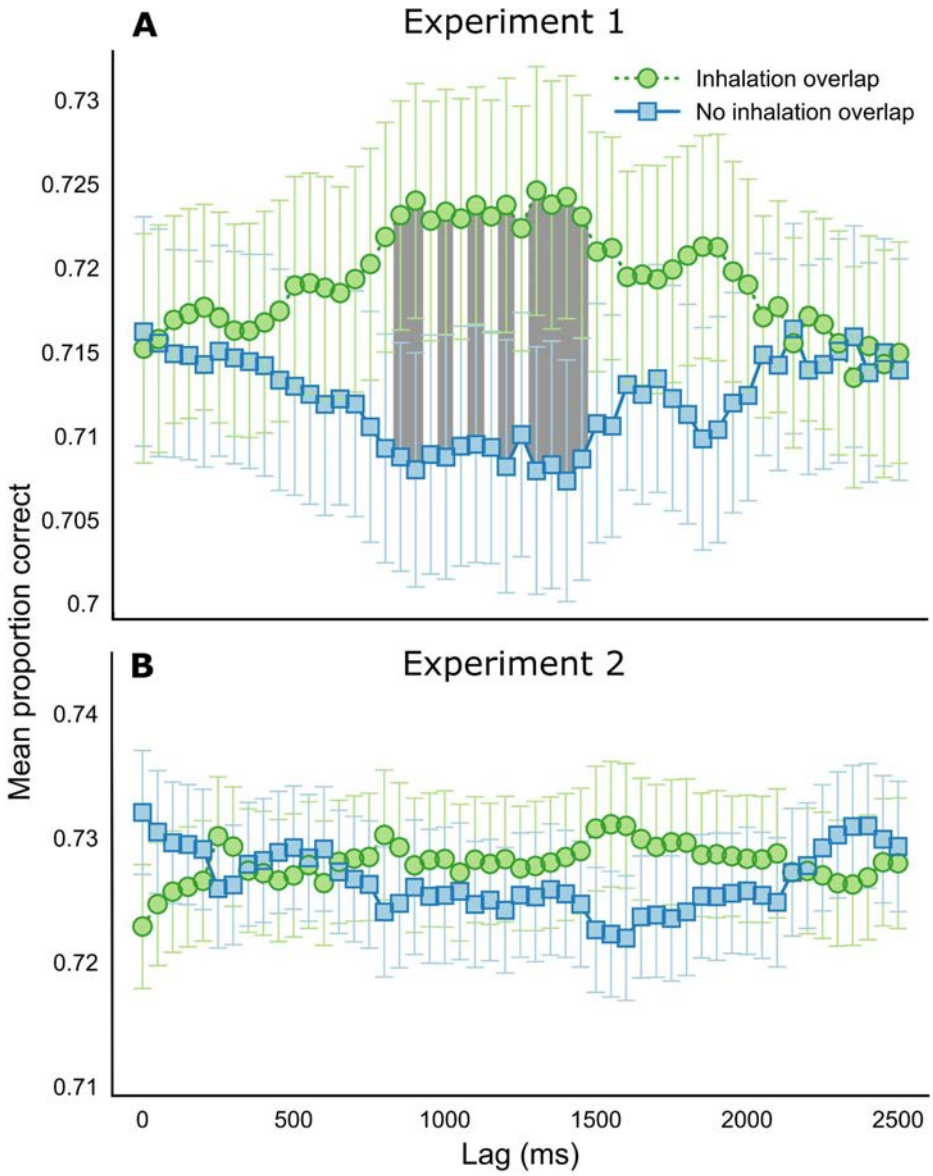

Figure 5.5. Lag analysis for Experiments 1 & 2. Participant-averaged identification performance on the memory task for repeated images that overlapped with inhalation as compared to those that did not. The lags represent the time delayed effects of breathing phase (lag = 0 corresponds to the main analysis). The gray areas mark statistically significant differences between *Inhalation overlap* and *No inhalation overlap* (uncorrected for multiple comparisons). The error bars indicate the standard error for the difference of means. **A)** The exploratory results from the first experiment. **B)** The pre-registered results from the second experiment.

In conclusion, neither **Study III** nor **Study IV** found any reproducible respiratory effects on performance in episodic visual memory tasks.

5.4 Study V: Do hormonal contraceptives influence chemosensory perception?

Hormonal contraceptive pills have been widely and effectively used since 1960. Despite its popularity, the use of OC has been associated with a variety of unwanted side effects that can lead to discontinuation of OC use. While some of these side effects have been confirmed, others might be propagated by hearsay and power of suggestion (Grimes & Schulz, 2011). As OC are an effective family planning tool, and discontinuation is associated with an increase in unwanted pregnancies (Rosenberg et al., 1995), it is important that people make the decision of whether to use OC on the basis of well-grounded facts. In this study, we set out to investigate potential side effects of OC use on chemosensory function. Whereas previous research in this area has mainly focused on the effects of OC use on the sense of smell, we extend this research by also investigating trigeminal and taste perception. Furthermore, we used a Bayesian approach to quantify the evidence in favor of the null hypothesis.

We assessed chemosensory performance in a group of women taking OC, and a control group of women who were not taking any hormonal contraceptives and had naturally regulated menstrual cycles of normal range. We found no performance differences among these groups for either odor, trigeminal, or taste sensitivity (see Figure 5.6), with Bayes factors favoring the null hypothesis for all tests (BF_{01} ranging from 3.23 to 3.63), except for odor identification performance, where the results were inconclusive ($BF_{01} = 0.98$).

Furthermore, we investigated whether the tastants quinine and sucrose were perceived differently between the two groups of participants. The participants scored the tastants along the dimensions of familiarity, pleasantness, intensity, and quality (see Figure 5.7). No group differences were detected; instead, the results favored the null hypothesis ($BF_{01} = 3.95$).

We concluded that it is unlikely that the use of hormonal OC affects chemosensory perception to a degree that is of ecological relevance.

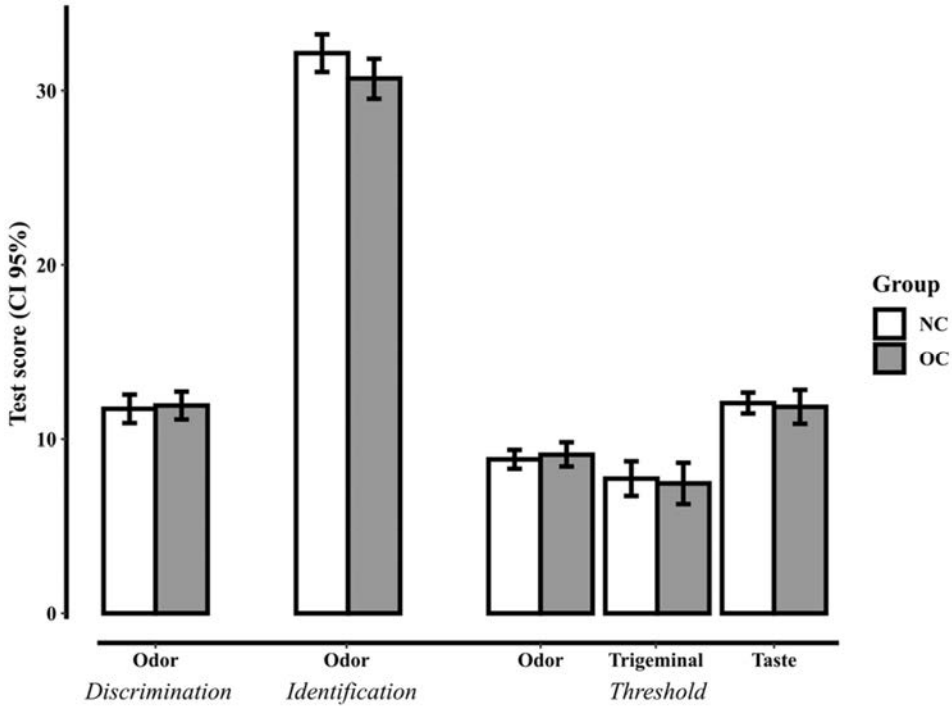

Figure 5.6. **Mean scores of the different sensitivity tests for NC women and women using OC.** Maximum possible scores were 16 for odor discrimination and odor and trigeminal threshold detection, 23 for taste threshold detection, and 40 for the odor identification task. Error bars display 95% confidence interval. NC = normal cycling; OC = oral contraceptives.

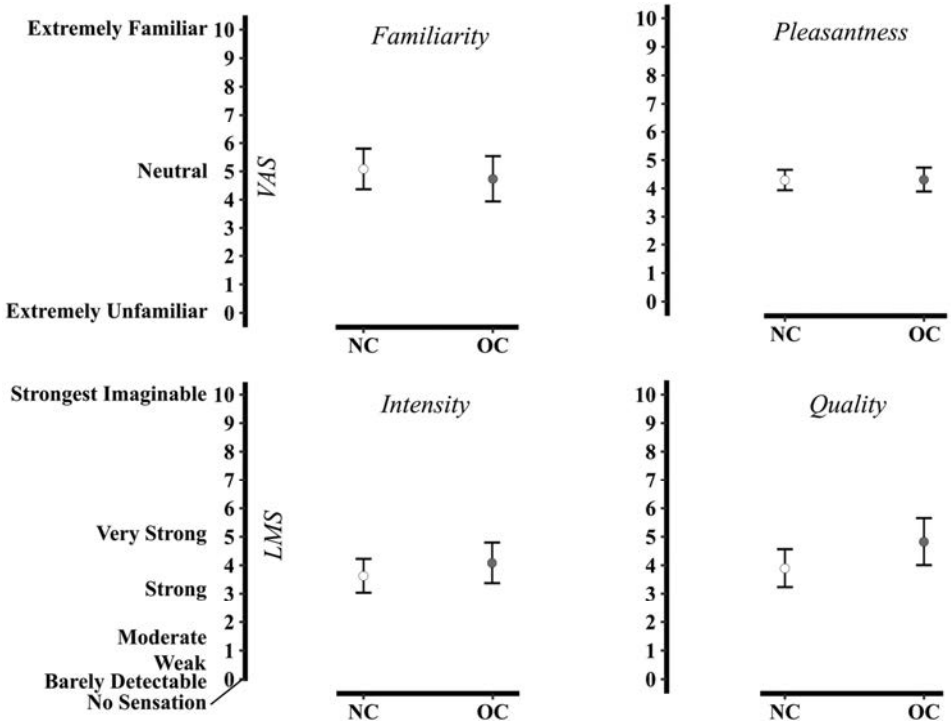

Figure 5.7. **Average perceptual ratings of tastants**. Participants rated the familiarity, pleasantness, intensity, and quality of sucrose and quinine. Error bars display 95% confidence interval. VAS = visual analogue scale; LMS = labelled magnitude scale; NC = normal cycling; OC = oral contraceptives.

6 Discussion

The overall aim of this thesis was to clarify and expand upon what is known about respiratory influences on pupil size dynamics and visual recognition memory. More specifically, we aimed to synthesize the research that has been conducted so far on respiratory influences on pupil size dynamics in humans (**Study I**), and then contribute to answering any identified outstanding questions empirically (**Study II**). Furthermore, we aimed to contribute to what is known about respiratory effects on performance in visual recognition memory tasks by addressing some of the identified shortcomings of previous studies and expanding upon them with new behavioral paradigms and extended measurements (**Studies III & IV**). Finally, we aimed to investigate whether hormonal oral contraceptives affect chemosensory sensitivity and perception (**Study V**).

In **Study I**, we discovered that the evidence for respiratory influences on pupil size dynamics in humans is less solid and extensive than what we expected. Not only was the underlying evidence for effects of breathing phase, depth, and rate on pupil size dynamics weak, but the influence of breathing route (oral or nasal breathing) had not been investigated at all. In **Study II**, we demonstrated small but significant effects of breathing phase on pupil size, and a potential for breathing rate to influence spurious correlations and phase synchronizations between the breathing and the pupil signal. Furthermore, we did not find any changes in pupil size in the time around inhalation and exhalation, and our results did not seem to change as a function of breathing route. **Study III** showed that breathing phase and route do not affect episodic visual memory differently, but that breathing does affect its underlying neurophysiology. **Study IV** revealed that breathing phase during nasal breathing has no effect on visual recognition memory when images are encoded using a rapid serial visual presentation task. Finally, in **Study V**, we show that oral hormonal contraceptives do not affect chemosensory sensitivity or perception.

In this chapter I will discuss the results from our studies, place them into context, and discuss their strengths and limitations, and perspectives for the future.

6.1 Does respiration influence pupil size dynamics: A simple question?

From the outset, we thought that the question of whether respiration influences pupil size was a relatively simple one. Based on the most cited literature, we expected to find good evidence proving that inhalation leads to pupil dilation and that exhalation leads to pupil constriction, with perhaps weaker evidence for effects of breathing route, depth, and rate on pupil size dynamics (Ashhad et al., 2022). Instead, our literature review (**Study I**) showed that in more than 50 years of research, only 12 studies had directly investigated any respiratory influences on pupil size dynamics. These studies varied greatly in their methods and methodology, and generally employed very small sample sizes, with a trend for null findings in the studies that had larger sample sizes. While our study did not reveal evidence against respiratory influences

on pupil size, it certainly showed that the underlying evidence is not very strong. Furthermore, the variety of methods used, and parameters studied, indicated that whether respiration influences pupil size is perhaps not such a simple question after all. Generally, it called for a more rigorous and systematic approach to answer the many outstanding questions.

6.2 Respiration influences pupil size but in a subtle and complex manner

With **Study II**, we confirmed that breathing phase influences pupil size, showing that pupil size varies in a small but systematic manner across the breathing cycle. However, the direction of our results is the opposite of what previous studies have shown, by demonstrating larger pupils around exhalation onset and smaller pupils around inhalation onset. More specifically, instead of dichotomizing the breathing cycle into in- and exhalation, we show how pupil size changes over the course of the breathing cycle by dividing it into 18 evenly spaced bins. This finer division of the breathing cycle allows for a much smoother demonstration of how the pupils change over the course of the breathing cycle and is also more in line with the demonstrated complexity of the different (and still contested) breathing phases (Krohn et al., 2023). To see how robustly the variations in pupil size are coupled to specific parts of the breathing cycle, replications are needed.

The complexity of the interaction between breathing and pupil size dynamics was further revealed by the discovery of a seemingly spurious correlation and phase synchronization between the breathing and the pupil signal, that is heavily influenced by the breathing rate. We hypothesize that this is driven by the sinusoidal nature of the breathing signal, and that a more slowly oscillating sinus wave inherently causes larger correlation and phase synchronization values than sinus waves of a higher frequency. I later tested and confirmed this hypothesis by demonstrating that slow sine waves correlate more strongly with the pupil signal from our study, than faster sine waves (see Figure 6.1). This spurious correlation might give the impression that breathing, and pupil size are more strongly correlated than they actually are. If for example, you compare the correlation between breathing and pupil size with the correlation between a scrambled breathing signal and pupil size, you will almost guaranteed get a significantly lower correlation value, but it is not a valid comparison. We solved this by comparing the correlation and phase synchronization between the breathing of a participant with their own pupil signal, and the pupil signal of all other participants. This way we revealed that a small but significant correlation and phase synchronization between breathing and pupil size does exist, that goes beyond the spurious interaction. We hypothesize that this spurious relation between breathing and pupil size, and the small effects that we found, are part of the reason why previous studies have only resulted in inconclusive evidence regarding the impact of various breathing parameters on pupil dynamics. Furthermore, we extended the research to also covering the impact of breathing route on pupil size dynamics, but we discovered no evidence that nose breathing affects pupil size differently than mouth breathing.

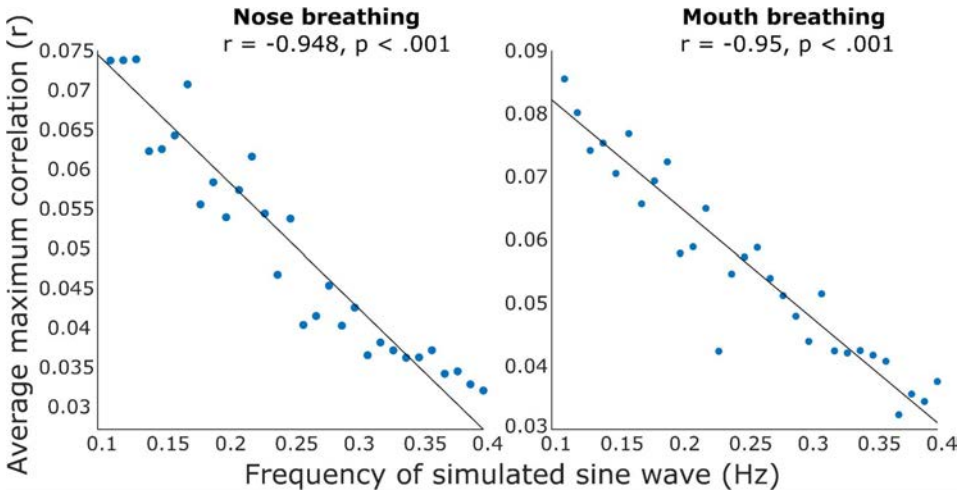

Figure 6.1 Strength of correlation between pupil size and simulated sine waves of various frequencies. I calculated the average correlation strength between clean sine waves (no noise) in the frequency range of human breathing observed in our study, and the measured pupil signal of our participants. The results confirmed that slower sine waves correlate on average more strongly with the measured pupil signal than faster sine waves. This held true for both the pupil signal of participants breathing through their nose and mouth.

6.3 Does respiration affect visual recognition memory performance?

A series of recent studies has investigated respiratory influences of visual memory, with mixed results (Huijbers et al., 2014; Johannknecht & Kayser, 2022; Nakamura et al., 2018, 2022; Zelano et al., 2016). We set out to clarify the respiratory influences on visual memory by improving and expanding upon previously used methods.

Study III had three main strengths compared to the previous studies. First, we made use of a within-subjects design to test possible effects of breathing route, where participants performed the same task twice, once while breathing through the nose, and once while breathing through the mouth. Second, we phase-locked the stimuli presentation to either inhalation, or exhalation onset during both the encoding, and the recognition phase, thereby investigating the potential effects of breathing phase onset more thoroughly. Third, we simultaneously recorded EEG activity, allowing for the investigation of brain activity underlying memory processes.

We found no effect of breathing route or breathing phase on performance in the visual memory task, but a potential effect of breathing phase on the participants' response bias as measured by the criterion, indicating that our participants had a tendency to answer more conservatively during exhalation compared to inhalation. Furthermore, we found that both breathing phase and breathing route affected the amplitude of the LPE component during encoding, whereas there were no, or inconclusive effects on the LPE component during recognition, or on the FN400 component during either phase. These results add to previous findings of respiratory influences on brain activity underlying memory functions (see Heck et al., 2019), but also

showed that this modulation of brain activity does not necessarily translate to behavioral effects.

However, **Study III** also had several limitations. First of all, similar to previous studies, with only 25 participants, the sample size was relatively small. Second, we lacked trial-by-trial knowledge during encoding, and therefore could not correlate the shape of the ERP components during encoding to later performance. Therefore, we could not analyze how respiratory influences on the LPE component during encoding affected later performance on a trial-by-trial basis. Third, our limited number of trials did not allow for further controls, such as non-phase-locked, or cross-phase-locked (inhalation during encoding and exhalation during recognition and vice versa) presentation of stimuli, or a non-restricted breathing block.

To expand upon these results and address shortcomings of statistical power, we designed **Study IV** with a focus on rigorous methods and the slogan "less is more" in mind. Also **Study IV** had several main strengths compared to previous studies. First, we had a sample size far greater than any previous study on this topic. Second, we performed a pre-registered replication experiment to see whether the results of our exploratory analysis could be replicated. Third, we made use of a rapid serial visual presentation repetition paradigm that relies on several aspects of basic visual processing and memory and thus should have a better chance of showing a breathing phase effect than the previously used visual memory tasks. And finally, we limited our investigation to two specific questions, thereby keeping high statistical power and the focus of the study, rather than performing a flurry of various tests.

The first question we asked was whether breathing phase influences memory performance. Specifically, we tested whether repeated images presented during inhalation would be remembered better than repeated images that were presented during a different part of the breathing cycle. The results showed that there was no difference in task performance for the repeated images that were presented overlapping with the inhalation phase, compared to the repeated images presented without overlap with the inhalation phase. Our second question was whether there is a delayed effect of nasal inhalation on cognition or perception. Therefore, we conducted an exploratory analysis where we tested for delayed effects of up to 2.5 seconds following inhalation, in steps of 50 ms. This approach led to significantly better performance for repeated images presented around one second after inhalation, compared to repeated images presented at other times during the breathing cycle. Because this second question was an exploratory one, we pre-registered and performed a replication experiment with an even larger sample size. In this larger second experiment, the exploratory findings could not be replicated and were therefore considered spurious, whereas the null finding of the first experiment was replicated. This is by far the most robust study that has been done to investigate breathing phase effects on visual memory so far, and it did not discover any effects of breathing phase on memory performance during rapid serial visual presentations.

Furthermore, the spurious result from the first experiment highlights the importance of replication studies, as well as properly pre-registered analyses and hypotheses. We had quite a large sample size ($n = 72$), and the delayed effect of inhalation made a lot of sense to us,

considering that potential inhalation driven oscillations generated in the OB take time to travel to further downstream areas of relevance, such as the hippocampus or the visual cortex, to influence visual processing streams. Given the pressure to publish, and the fact that it is easier to publish significant results than null findings (Ferguson & Heene, 2012; Matosin et al., 2014; Song et al., 2017), there are strong incentives to skip the hassle of going through another round of data collection to verify exploratory findings.

Thus, both our studies investigating respiratory influences on visual memory did not find any performance effects. While these studies are far from covering every potential aspect of breathing on visual memory, they do question the validity of such findings, and advocate for rigorous methods to investigate the details of potential respiratory effects of breathing on visual memory performance.

6.4 Do hormonal oral contraceptives affect chemosensory perception?

Research has shown that odor perception fluctuates over the course of the menstrual cycle (Grillo et al., 2001; Lundström et al., 2006; Martinec et al., 2014), it would therefore not be surprising that taking medication that disrupts the natural menstrual cycle, also leads to changes in odor perception. Indeed, several studies have reported that OC influence odor perception (Caruso et al., 2001; Derntl et al., 2013; Kollndorfer et al., 2016; Lundström et al., 2006; Renfro & Hoffmann, 2013). However, their results have been mixed and sometimes contradictory. We aimed to assess potential influences of OC on chemosensory perception in general, by extending the research from odor perception to including potential influences on trigeminal and taste perception. The main strengths of this study, beyond the inclusion of the trigeminal and taste sense, were our use of Bayesian statistics to allow for the assessment of the null hypothesis, and the careful selection of tastant and odor stimuli to cover a wide variety of features such as odor complexity, and ecological relevance.

Our results showed no evidence of chemosensory perception being affected by the intake of OC, with our data either supporting the null hypothesis or being inconclusive.

However, despite its strengths, the current study also suffers from various limitations. First of all, similar to previous studies, the sample size was rather small and therefore we did not have enough power to detect potentially very small effects. Furthermore, the type and dosage of the hormonal contents, and duration of intake of the used OC varied. Finally, despite our careful selection of stimuli, we were limited in the amount of different stimuli we could test. Therefore, additional research is needed to confirm our current findings of no effects of OC on chemosensory perception, to address these specific shortcomings. However, given the inconclusive and contradictory previous results, and our current null findings, we conclude that an effect of OC on chemosensory perception is unlikely and, if present, presumably of a small effect size with negligible ecological relevance. This should come as good news to the many users of OC as, based on these results, there is no need to be concerned about altered chemosensory perception.

6.5 Overarching considerations and reflections

6.5.1 The need for rigorous methods

The field investigating respiratory influences on perception and cognition has in the past few years grown rapidly and gained a lot of attention. Much has changed and many exciting discoveries have been made since the start of my PhD. However, the studies investigating potential respiratory influences on human behavior have been characterized by small sample sizes and a great variety of methods (our **Study III** also suffers from this). In an attempt to advance our knowledge, studies generally focus on investigating new, and many questions at the same time. While it makes sense to build upon previous knowledge and to further develop one's methods (we have done this continuously throughout the studies included in this thesis), it has also led to a wide variety in study outcomes that are difficult to summarize and often contradictory.

If we take the question of whether breathing phase influences visual recognition memory as an example. We have an initial finding of Huijbers et al. (2014), showing that participants spontaneously phase-lock their respiratory cycle to stimuli during encoding and that the stronger the phase-locking, the higher the probability for the stimuli to be recognized. This was followed by another study which showed a positive effect of nasal inhalation on episodic visual memory (Zelano et al., 2016). However, both we (**Study III**), and others (Johannknecht & Kayser, 2022) could not replicate this effect. Furthermore, another group demonstrated the opposite of this effect, with nasal inhalation being associated with lower performance in a delayed match-to-sample visual recognition task (Nakamura et al., 2018, 2022). And finally, our **Study IV**, found no effect of breathing phase on performance in another visual recognition memory task. Here we have seven studies investigating the effect of breathing phase on visual recognition memory, using four different paradigms (seven different ones if you are strict, because even the repeated paradigms were slightly modified), using various methods to measure and categorize breathing, and besides **Study IV**, the highest sample size number after accounting for exclusion of certain participants, was 25. Taken together, this means that there is still much to address and clear up.

What the field now needs are more systematic and rigorous studies of which I believe **Study IV** to be a good example with its large sample size, replication, and pre-registration. But also, the study by Kluger and colleagues (2023), who combined data from several studies and labs to achieve a high sample size for their neuroimaging study, is a good example of how combined efforts can achieve more (Kluger et al., 2023). Also, the studies of Mizuhara and Nittono deserve credit for being the first registered reports in this field, which is a good way to avoid questionable research practices (Chambers & Tzavella, 2020; Mizuhara & Nittono, 2022, 2023; Wiseman et al., 2019).

6.5.2 The double-edged sword of simplification

The human body is incredibly complex, so we often use reductionist methods to study it. Such an approach is no exception when researchers have investigated the influence of respiration on cognitive and perceptual processes. For example, researchers often divide the breathing cycle into inhalation and exhalation, assume that people breathe mostly through their nose, and ignore individual differences in breathing frequency and depth across participants and study duration. Furthermore, many hypotheses in this field are based on simplistic interpretations of foundational research. We, too, have made some of these simplifications in our research, and I believe they have been helpful to get this field going and generate exciting ideas. However, I believe that this field is now at a stage where we need to move beyond these simplifications and start to focus on the details if we want to resolve some of the contradictory findings that have been published so far. Some steps in the right direction include assessing effects across the entire breathing cycle, as done in **Study II** or in the study by Kluger et al. (2021), and controlling and investigating specific breathing rates (see for example D'Agostini et al., 2022). These approaches will help us to develop a more nuanced understanding of how respiration influences cognition and perception.

As the respiration signal has long been ignored or interpreted as noise (Krüger & Glover, 2001), the research into respiratory influences on perception and cognition is actually part of a movement trying to go back from simplifying our view of how the body works, by considering how our brain responds to external stimuli in light of internal states and processes, rather than focusing on the external stimuli exclusively (see for example Brændholt et al., 2023; Heck & Varga, 2022). As science over time advances to allow for more detailed and complex research, my awe for the intricacies of the body and brain keeps growing.

6.5.3 The importance of publishing null findings

Four out of the five studies included in this thesis present null findings as their main study outcome. Whereas this can be perceived as less exciting than positive results and is not necessarily the outcome I had hoped for at the start of my PhD, it now fills me somewhat with pride that we are putting in the effort to get these null findings out of the confines of our research group and into the scientific literature. There is an excess of positive results in the psychology literature (Scheel et al., 2021), and a publication biased against negative results has been observed in both peer review (Atkinson et al., 1982; Mahoney, 1977), and in investigators themselves (Franco et al., 2014, 2016). However, when null findings are not published, it becomes impossible to accurately weigh the evidence for existing paradigms, and a systematic bias in what research gets published, prevents accumulative science from accurately inferring what is true about the world. In general, the field of psychology has undergone what has been called a crisis (Giner-Sorolla, 2019), revolution (Spellman, 2015; Vazire, 2018), or renaissance (Nelson et al., 2018), in the 2010s when it comes to scientific research practices (for review see Nosek et al., 2022). Therefore, a willingness to pursue and accept the publishing of null findings by supervisors and scientific journals is perhaps a sign that the field is moving in the right direction.

7 Conclusions

The overall aim of this thesis was to enhance our understanding of how respiration influences pupil size dynamics and visual recognition memory. The key takeaways are the following:

The research into respiratory influences on pupil size dynamics has been sparse, methodologically limited, and inconclusive. When accounting for previous limitations, my own research revealed that breathing does influence pupil size, but in a subtle and more complex manner than previously believed. The consistency and ecological relevance of these influences need to be determined by further research.

My research into respiratory influences on visual recognition memory did not reveal any effect of breathing phase or route on performance in visual episodic memory tasks. This challenges the notion of direct and unequivocal links between breathing and visual episodic memory, emphasizing the importance of implementing robust and high-powered studies with rigorous methods in the future.

Finally, the detour into whether oral hormonal contraceptives affect our chemosensory perception showed that they do not.

8 Future perspectives

My research has identified several key questions that require further investigation to fully comprehend the subjects of my thesis.

With regard to the influence of respiration on pupil size dynamics, the findings of **Study II** should first be replicated to verify the consistency of the specific observations regarding larger pupils around exhalation onset and smaller pupils around inhalation onset. Also, it would be of interest to investigate the influence of breathing on pupil size while participants are asked to breathe at various constant frequencies and/or depths. Considering the observed spurious correlation, investigating the influence of breathing on pupil size across a range of constant breathing frequencies and/or depths could elucidate whether the extent of this influence is modulated by our breathing rate. Furthermore, extending this work to determine whether these effects persist while participants engage in a visual task, rather than solely at rest, is important. If these effects are sustained during task engagement, their ecological relevance should be assessed by investigating whether they modulate performance in visual perception tasks. This could potentially provide an explanation for the previously observed changes in visual perception ability across the breathing cycle.

Future work on respiratory influences on memory should emphasize careful study design and focus on specific questions. The aggregated results from the various studies on visual episodic memory so far, are very unclear. If the field wants to pursue this further, large scale replication studies are needed to see which results hold true. Importantly, until now the memory paradigms used have been suboptimal to study whether respiration can affect memory. To do this, one would need to implement paradigms that more directly target hippocampus-dependent memory functions. One way to do this would be to study spatial navigation memory with mouth and nose breathing separately. Importantly, in animal research respiratory influences on hippocampal rhythms are strongest during freely moving spatial navigation or odor tasks. Thus, in combination with spatial navigation, it would be interesting to compare the effect of breathing across different sensory stimuli.

More generally, our understanding of the fundamental physiological mechanisms underlying respiration in humans remains incomplete. The majority of animal studies have been conducted on rodents whose respiratory anatomy differs significantly from that of humans. For instance, rodents cannot breathe through their mouths, and forced mouth breathing has detrimental effects on their health. In contrast, human anatomy not only permits mouth breathing but also optimizes it for speech production. Therefore, the effects of mouth and nose breathing on the human brain and behavior may be more similar than previously assumed. Furthermore, the extent to which airflow reaches the olfactory epithelium in humans during different stages of the breathing cycle remains unknown. Notably, airflow simulation studies have demonstrated that both nasal inhalation and exhalation reach the olfactory epithelium (Zhao et al., 2004, 2006), thereby influencing OSNs. If this is indeed the case, it would imply that in humans, both nasal inhalation and exhalation shape olfactory bulb activity, potentially influencing global

brain activity and subsequent behavior. These considerations raise the question of how heavily we can rely on animal data to draw inferences about human behavior.

Knowing the answers to these, and other basic questions, such as how much airflow is needed for the OSNs to be activated mechanically, would be of huge help in formulating more precise hypotheses regarding the potential influence of respiration on perceptual and cognitive processes.

Regarding the influence of oral hormonal contraceptives on chemosensory research, our findings provide preliminary evidence suggesting that our chemical senses are not affected by these contraceptives. However, due to the small sample size and heterogeneity in the type of oral hormonal contraceptives used, this question requires further investigation. Additionally, given the wide range of individual differences in chemosensory sensitivity, within-subject studies would be very informative. Does an individual's chemosensory perception change after starting or stopping the use of oral hormonal contraceptives? This question is intertwined with the broader topic of how our chemical senses are influenced by our hormonal system, a research area of significant relevance to everyone.

In conclusion, this thesis highlights the need for further research into how respiration affects human behavior. Replicating existing findings, refining experimental paradigms, and bridging the gap between animal and human studies are crucial steps in unraveling this complex interplay. Only then is it possible to understand how this fundamental physiological process, repeated 15-20 times per minute, can shape our behavior.

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Be good to your family, y'all

No matter where your families are

'Cause everybody need family, y'all

- Sunshine, by Mos Def

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