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Investigating an interplay between respiration and attention via the locus coeruleus - noradrenaline system

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Supervised by Professor Paul Dockree (TCD)

Declaration

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Summary

The idea that respiration and attention interact with each other has been central to yogic practices for millennia. Contemporary research in cognitive neuroscience is beginning to unravel remarkable ways in which respiration modulates, and is modulated by, cognitive processes. Mounting evidence is suggesting that our ongoing respiratory rhythm may act as a physiological pacemaker for higher order functions to be entrained by. Despite many sensory-cognitive domains being investigated from this perspective, the area of 'attention' specifically has been sparsely researched. However, one dynamical systems model (Melnychuk et al 2018) has attempted to bridge the gap between respiration and attention via the locus coeruleus- noradrenaline (LC-NA) system, due to the crucial simultaneous roles that the LC has in the arousal and attentional system as well as the brainstem respiratory network. The present thesis aimed to corroborate initial supporting evidence for synchronisation between these systems and test predictions of this model.

Empirical Chapter 1 aimed to test whether decreasing respiratory frequency would stabilise both behavioural attention and pupil diameter (PD) oscillatory activity, compared to a spontaneously breathing control group. PD was used as a proxy measure for LC activity. A novel task was designed, the Paced Auditory Cue Entrainment (PACE) task, in which participants responded rhythmically to auditory cues, providing a continuous measure of sustained attention, and additionally, the breathing group used the cues as a breath guide, breathing in the range of 0.1 – 0.15 Hz. Despite no group differences in the variation of the timing of responses, the control group committed significantly more frequent response rhythm inversions – an exploratory accuracy variable of pressing the wrong key at the right time. The breathing group barely committed any of such errors compared to the control group. Additionally, the PD activity of the breathing group closely followed the frequency of the breathing, such that they were oscillating in the same range, implying that PD and therefore possibly LC activity was entrained by the breath intervention. From this we conclude that decreasing respiratory frequency did indeed stabilise attention, mitigating lapses, possibly through stabilising fluctuations in LC activity.

Empirical Chapter 2 was an investigation into how attention is modulated over the respiratory cycle in a sustained attention task with no explicit respiration instructions. We used younger (YAs) and older adults (OAs) as a natural division of attentional strategy, since OAs were previously seen to show less mind wandering and more stable psychophysiological signatures of attention on this task than the YAs, however the groups sustained attention performance did not differ. We discovered here that both groups showed evidence of entraining their respiratory cycle to events in the task, however, the OAs did this to a significantly greater degree. Analysis of task performance, subjective attentional state, PD, and EEG oscillatory power, showed that all these attentional signatures were significantly modulated over the respiratory cycle. We were further able to utilise the differing attentional strategies, as well as the degree of respiratory-task entrainment, to infer the relative contributions from top-down and bottom-up influences respectively on these modulatory patterns. There appeared to be a fluctuation in attention so that conditions were optimal for task focus during the respiratory phases which were most entrained to task events, and less optimal for task focus and more geared towards mind wandering outside of the entrainment window. We interpret these findings to be evidence of respiration as an 'attentional metronome' of sorts, interacting with each other via the LC-NA system.

Empirical Chapter 3 utilised the data from the prior chapters to investigate how sighs (infrequent, deep breaths) are implicated in resetting suboptimal respiratory variability, corroborating previous findings, as well as testing for implications in transitioning between attentional and arousal states. Sighs here did play a significant role in resetting respiratory variability; however, no evidence was found that behavioural or experiential measures of attention were influenced. A significant association was discovered between the degree of respiratory-task entrainment and sighs, suggesting that sighs may in part function to reset entrainment-induced random respiratory variability, and facilitate further entrainment. PD was seen to undergo large changes over the course of sighs, implicating the LC-NA arousal system in sigh behaviour in humans.

Collectively, this thesis provides evidence supporting a linkage between respiration and attention via the locus coeruleus, as well as providing novel methodologies to investigate this relationship further.

Acknowledgements

This PhD turned out to be an incredibly introspective endeavor as the topic encouraged me to constantly analyse my own thought and breathing patterns, as well as learning so many new research skills. But I could only perform this inward dive safely with the knowledge that I had many people supporting me.

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Michael Melnychuk, your ambition to apply the neuroscientific method to these crucial yogic ideas matches my own, and I am so glad that you walked this path before me so I could benefit so vastly from your tools and insights. I thoroughly enjoy exploring ideas and marrying these scientific and spiritual worlds with you, and I very much look forward to working together in the future.

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Thesis Introduction

Introduction

Our breath undulates alongside our conscious experience throughout our lives, which is an intimacy well recognised by the yogis. In his book 'Light on Yoga', influential yogi B.K.S. Iyengar says: "The yogi's life is not measured by his [their] days, but by the number of his [their] breaths" (Iyengar, B. K., 1966). Parallels have often been drawn between the undulating nature of the breath and that of the mind, for example: "When the Breath wanders, the mind is unsteady, but when the Breath is still, so is the mind still." (Svātmārāma, circa 1400 C.E.). "If our breathing is light and calm—a natural result of conscious breathing—our mind and body will slowly become light, calm, and clear, and our feelings also." (Nhất Hạnh, Thích, 1998). "When the mind is agitated, change the pattern of the breath." (Patanjali, early centuries C.E.). The regulation of breath with the intention to regulate the fluctuations of the mind is referred to as Pranayama. Within Patanjali's Sutras, the seminal formalisation of the "eight limbs" of yoga, Pranayama is the fourth limb, and the practice is stated to be a prerequisite for the sixth limb, named 'Dharana', which is best translated as 'concentration' (*Yoga Sutras of Patanjali 2.49-2.53*, n.d.). Accordingly, central practices of yoga which seek to expand conscious awareness, revolve around this interplay between breath and attention.

Despite the centrality and enduring nature of this breath-attention interplay in human culture, it has been remarkably understudied within cognitive neuroscience. Yoga is primarily a first-person science where the individual experiments on themselves. In contrast, neuroscience is conventionally a third-person science, seeking to demonstrate effects on groups in the population and is generally accepted in modern times as drawing valid and more easily observable conclusions. The present thesis is a neuroscientific investigation into this yogic idea with the intention of elucidating whether we can explain a relationship between the breath and attention from this modern perspective.

Elucidating the mechanisms driving our attentional fluctuations is a pressing matter in modern society. The United Nations (UN) has recognised that we are living in an "attention economy" (Nations, n.d.). This term describes how the abundance of information available, particularly on the internet, is saturating our attentional capacity, and how marketers strategise to overcome this limiting factor with just the right degree of engaging content. With our attention being pushed to its limit and treated as a commodity, it seems vitally important to understand how to gain greater autonomy over our attention. An organic interoceptive signal like the breath seems like an appropriate antidote. The severity of this issue is only exacerbated for those diagnosed with disorders that can negatively impact attentional abilities such as attention deficit hyperactivity disorder (ADHD) or autism spectrum disorder (ASD). Crucially, the breath is a universally accessible tool and engaging with it through various exercises have been shown to have positive effects on psychological wellbeing (Balban et al., 2023; Fincham et al., 2023; Zaccaro et al., 2018). Interestingly, disordered breathing has been implicated in ADHD and ASD which makes it a suitable therapeutic target for these individuals also. For example, there is a strong link between those with ADHD symptomatology and sleep disordered breathing such as mouth breathing, snoring or apnoea (Kalaskar et al., 2021; Schredl et al., 2007; Sedky et al., 2014). In ASD, respiratory dysrhythmias are observed such as Cheyne-Stokes and Biot’s respiration (irregular rate and depth interspersed with apnoea) (Ming et al., 2016), as well as a decreased respiratory sinus arrhythmia (the degree of heart rate variability that is in synchrony with respiration) (Sheinkopf et al., 2019). Additionally, a left nasal dominance of airflow has been reported in ASD (typically expected to alternate in balance) (Dane & Balci, 2007). The comorbidity of attention and breath disorders suggests that problems of breathing may be consequential for attention and not merely epiphenomenal.

In the last decade there has been a surge of interest in respiration within cognitive neuroscience. This body of work has shown that certain cognitive processes, as well as oscillatory brain activity, appear to be modulated by the rhythm of respiration. This gradual integration of the role of respiration in cognitive function represents a broader shift towards viewing cognition as embodied. The traditional view of cognition being a “brain-centric” process that is dissociable from the sensory and motor systems is challenged here. Instead, it appears as though a full account of cognition would be incomplete without the consideration of, for example, the information provided by bodily signals from the cardiovascular, digestive (Azzalini et al., 2019), and respiratory (Heck & Varga, 2023; Varga & Heck, 2017) systems.

Before discussing in greater detail the evidence and emerging theoretical frameworks for an inherent respiratory-cognitive relationship with an emphasis on attention, it is worth introducing the topics of respiration and attention in isolation.

Respiration

It is telling that the Sanskrit word ‘prana’ used by the yogis simultaneously means ‘breath’ and ‘vital life force’. Inhaling air is the first act in life and exhaling is the last, and the cessation of breathing would terminate life many magnitudes faster than that of eating or drinking. Respiration, as it is conventionally referred to in neuroscience, serves to maintain an optimal homeostasis of O_2 and CO_2 levels in the blood which then perfuses into bodily tissues to meet metabolic needs (Clancy & McVicar, 1996). Respiration is automatically maintained through the activity of central pattern generators in the brainstem (Krohn et al., 2023), with the preBötzinger complex being considered the most vital as it drives inspiration (Gray et al., 2010). Expiration is a passive process during quiet rest and becomes active under greater metabolic demand such as during vigorous exercise (Ramirez et al., 2014). In addition to mediating vital gas exchange, respiration has to be modulated to carry out a number of important bodily functions such as during coughing, sneezing, hiccupping, or swallowing (Trevizan-Baú et al., 2024).

Beyond biological necessity, there are actually few areas of life where respiratory modulation is not implicated. The social fabric of humans is largely based upon our ability to modulate respiration to produce complex speech, as well as expressing emotions such as laughter, crying, or surprise. Human culture is enriched with acts of musical feats such as singing or playing instruments which require fine respiratory control. And as priorly mentioned, modulating respiration has been central to exploring altered states of consciousness for millennia within meditative practices. Therefore, to appreciate the advanced capabilities of human beings is to also appreciate how they have evolved in lockstep with complex interactions with the respiratory system. It is therefore no surprise that there is a complex integrated network of many brain areas that influence respiratory control (Krohn et al., 2023).

For respiration to interact with these higher order functions, there should be communication with areas above the brainstem. Respiratory information is encoded in the olfactory cortex, somatosensory cortex, and insular cortex to encode olfactory, ventilatory and interoceptive information respectively (Heck et al., 2017; Kluger & Gross, 2020; Krohn et al., 2023). Motor and premotor areas of the cerebral cortex play a key role in coordinating volitional respiratory activity, whilst being possibly able to override brainstem activity here (Pouget et al., 2018; Trevizan-Baú et al., 2024). Respiratory modulation during emotional expression also implicates the limbic system in coordinating respiratory activity (Homma & Masaoka, 2008; Masaoka et al., 2014). Here, the amygdala coordinates fear responses induced by changes in CO_2 (Ziemann et al., 2009) and the dorsomedial hypothalamus coordinates stress-induced respiratory behaviour (Bondarenko et al., 2015).

Recent research suggests that interactions between respiration and higher areas are bidirectional. Gamma frequency neural oscillations in widespread cortical and limbic regions were seen to be modulated by attentive and volitional respiration (Herrero et al., 2018). Widespread cortical areas overlapping with canonical brain networks have been seen to be modulated by ongoing respiration during quiet rest using magnetoencephalography (MEG) imaging (Kluger & Gross, 2021) (Figure I.3). And respiratory modulation of brain oscillations during tasks has been reported within the limbic system (Zelano et al., 2016), and outside of it (Nakamura et al., 2022; Perl et al., 2019).

Although we understand the necessity of respiration for vital gas exchange and other biological functions, we are only beginning to unravel the implications of respiration interacting with higher order brain areas and processes. Elucidating this may be critical to understanding how information processing is organised in the brain and potentially orchestrated by peripheral signals like respiration.

Attention

Our notion of how attention functions in the brain has undergone significant developments in the last 40 years. Posner & Petersen in 1990 formalised the idea that attention was something grounded in neural activity, identifying an “attention system” comprised of various brain areas with regional specificity in how they interact with other cognitive systems (Posner & Petersen, 1990). In their view, the attention system could be divided into subsystems according to distinct but interrelated aspects of attention: alerting, orienting, and target detecting. “Target detecting” has since been developed into the concept of executive control and is greatly attributed to activity in the frontoparietal network (Marek & Dosenbach, 2018; Petersen & Posner, 2012). Sustained attention, the focus of the present thesis, was considered by the authors to be the maintenance of an alert state, which would act to decrease the time for orienting to and detecting targets. To use the common analogy at the time, sustained attention was like keeping a “spotlight” turned on, which could rapidly identify a target within the focal location, or quickly reorient to a new location if needed. This process was thought to be supported by the locus coeruleus – noradrenaline system (LC-NA) due to its fundamental role in modulating global arousal (Berridge, 2008).

Since the conception of this model, evidence from directly accessing the LC (Aston-Jones & Cohen, 2005b) as well as indirect evidence in humans using pupil diameter as a proxy measure (Algermissen et al., 2019; Brunyé et al., 2023; Gilzenrat et al., 2010; Hayes & Petrov, 2016; Jepma & Nieuwenhuis, 2011; Regnath & Mathôt, 2021) have confirmed a fundamental role for the LC-NA system in sustaining and shifting attention.

Although the core principles and brain regions implicated in an attention system have been well conserved since this models conception (Petersen & Posner, 2012), advancing methodologies have elucidated a more dynamic and complex account of how attention is sustained (Esterman & Rothlein, 2019; Fortenbaugh et al., 2017). Attention is neither constant over time, nor does it show simple linear decrements, but rather it fluctuates moment-to-moment (Esterman et al., 2013). Recent work has shown that the timescale of attentional fluctuations may be even faster than previously considered. Even when attention is perceived to be focused on a fixed point, it is not strictly a continuous process, but instead, appears to sample the environment in a rhythmic fashion (Fiebelkorn & Kastner, 2019). Rather than sustained attention being akin to a static spotlight, it is more like a light which fades in and out every few seconds or minutes, as well as flickering on and off many times a second.

A “rhythmic theory of attention” (Fiebelkorn & Kastner, 2019) was derived from experiments which largely investigated the detection of visual, spatial information (Busch & VanRullen, 2010; Fiebelkorn et al., 2013, 2018; Helfrich et al., 2018; Landau et al., 2015; Landau & Fries, 2012). In these studies, detection of visual targets was dependent on the pre-stimulus phase of theta oscillations in the frontoparietal network , implying a theta-rhythmic sampling of objects despite perceived fixed focus. It was also seen that attention reorientates between different locations, also at theta frequency (Dugué et al., 2016; Landau et al., 2015). Therefore, Fiebelkorn & Kastner (2019) suggested that attention oscillates at theta frequency, with some phases being optimal for attentional sampling of the current focus, and others being optimal for attentional shifting. During opportunistic phases for attentional sampling, sensory processing is enhanced and motor systems are suppressed. During opportunistic phases for attentional shifting, sensory processing is diminished and motor processes are enhanced. One function of theta-rhythmic attentional sampling is suggested to be avoiding conflicts between sensory and motor processing by separating them to different states of theta oscillations. A further crucial suggested function is that this should also facilitate attentional flexibility by providing these opportunities windows for attentional reallocation on a cyclic basis. Attention does not necessarily reorientate at theta phases which are conducive for doing so, but rather, the relevant systems are attenuated or primed to provide the opportunity. This should avoid the pitfalls of either overexploiting a point of focus, or constantly shifting between options – a dilemma known as the "explore-exploit trade-off" (Addicott et al., 2017).

Causal evidence for this rhythmic theory of attention was reported very recently from observations of patients with frontal and parietal lesions, compromising regions in the frontoparietal network (Raposo et al., 2023). This study showed that reaction time in a visuo-spatial attention task fluctuated as a function of the interval between pre-target cues and the targets in both healthy controls and lesion patients, corroborating the idea that attention samples spatial information rhythmically. Crucially, patients exhibited high amplitude, theta (frontal lesions) and alpha/beta (parietal lesions) brain oscillations proximal to lesions (a common post-lesion finding, e.g. Cassidy et al., 2020), which were correlated to a higher amplitude in their behavioural fluctuations (greater range of variation in reaction times) at these frequencies compared to healthy controls. Therefore, these data show strong causal evidence that low-frequency neural oscillations in the frontoparietal network are functionally related to rhythmic attentional sampling at the same frequency. These findings also imply an extension of the range for attention sampling into high alpha/low beta. It has also been seen that task difficulty modulates the attention sampling frequency, and thus, strict frequency ranges are probably inaccurate (Chen et al., 2017)

Fiebelkorn & Kastner (2019) also contextualised this theta-rhythmic attentional sampling with the activity in other neural frequency bands. For example, synchronisation in gamma band activity is related to enhanced sensory processing (Strüber & Herrmann, 2022), and it has been reported that theta-dependent increases in gamma activity were related to better target detection (Landau et al., 2015). Therefore, the phases of theta which are conducive to sensory processing appear to be complemented by enhanced gamma synchronisation. In further complement, one could expect increased beta synchronisation in the enhanced sensory, attentional sampling theta phases due to its association with motor suppression (Barone & Rossiter, 2021). Alternatively, alpha synchronisation is related to sensory attenuation (Foxe & Snyder, 2011), and thus could be expected during theta phases associated with attentional shifting. Therefore, there could be a complex coordination of activity across frequencies that support rhythmic attention. As is discussed in more detail further on, respiration also has phase-amplitude coupling relationships with higher frequency brain oscillations. Respiration could potentially be included into this model as a frequency slower than theta which is also modulating attention on a rhythmic basis, providing opportune windows for attention sampling and attention shifting.

Another key area in the attention literature which has received prominence in recent years is how attention shifts between externally directed task focus, and internally directed mind wandering (Smallwood

& Schooler, 2015). Research here has considered how attention does not simply reorientate between different task-related goals, but instead, a considerable amount of time is spent in states where attention is internal and often unrelated to ongoing external tasks –around half of the time by some estimates (Killingsworth & Gilbert, 2010; Seli, Beaty, et al., 2018). mind wandering has primarily been detected utilising experience sampling thought probes during cognitive tasks, probing the subjective nature of participants' attentional state (Weinstein, 2018).

In addition, advances have been made in probing the physiological background conducive for various mind wandering states. Using pupil diameter (PD) as a measure of arousal and proxy for LC-NA activity, it has been shown that mind wandering is concomitant with relatively low or high PD (Franklin et al., 2013; Grandchamp et al., 2014; Groot et al., 2021; Pelagatti et al., 2018, 2019; Unsworth & Robison, 2018), with the former associated with low arousal inattentiveness and the latter with high arousal distractibility (Unsworth & Robison, 2016, 2018). This is thought to reflect the inverted U-shaped relationship between LC-NA tonic activity and attention, where an intermediate level is optimal for task focus due to intermediate arousal levels and the facilitation of LC phasic activity which are locked to behaviourally relevant task events (Aston-Jones & Cohen, 2005b). LC phasic bursts are therefore thought to selectively enhance the active brain regions supporting task-relevant cognitive processes, and can be inferred through observing evoked PD activity (Gilzenrat et al., 2010; Joshi et al., 2016). These task-related

PD responses have been seen to be diminished during periods of mind wandering (Smallwood et al., 2011) which suggests that perceptual decoupling of attention to the external task occurs here (Schooler et al., 2011). Studies measuring the electrophysiological correlates of mind wandering have corroborated this idea, showing diminished amplitude in event-related potentials (ERPs) (Kam & Handy, 2013). Additionally, greater low-frequency oscillatory power (delta, theta, alpha) is observed during mind wandering, particularly in frontal regions (Kam et al., 2022). Both areas of findings are indicative of an attenuation of sensory processing, presumably to minimise interference with internal mentation.

Akin to how sampling attention at theta frequency should facilitate attentional flexibility, oscillating between task-related focus and task-unrelated mind wandering should achieve the same. This was well described by Sripada (2018), positing a mind wandering-focus oscillation as an explore-exploit trade-off. An optimal strategy for achieving long-term goals would reap the benefits from both exploring alternative ideas, as well as exploiting present ones. The author further suggested that the LC-NA system would be a fitting candidate to mediate oscillations between these attentional modes, due to its role in modulating arousal and attention as priorly discussed.

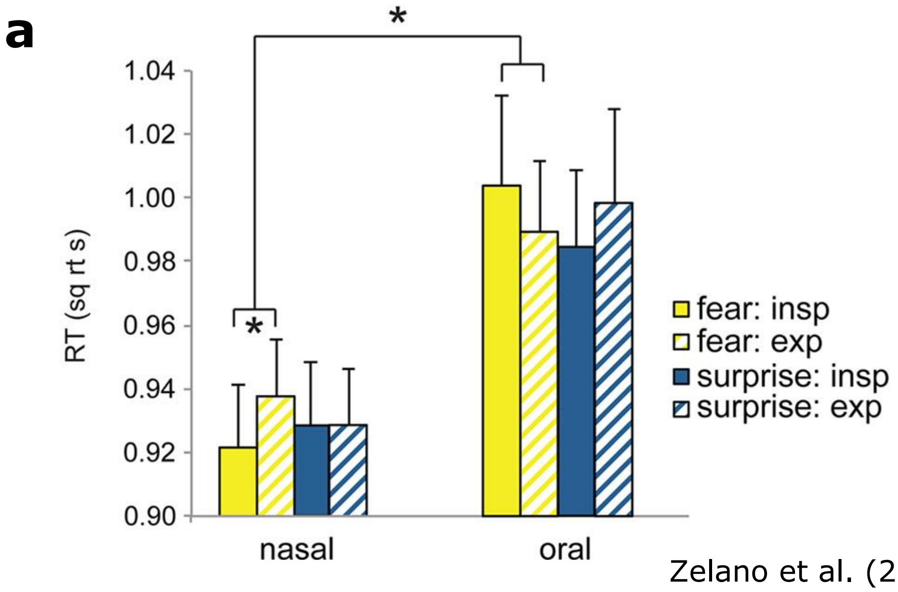
In conclusion, research into attention has evolved our understanding from perceiving it as a static, continuous process, as a highly dynamic one that oscillates over different time scales. Attention appears to sample the environment multiple times a second, providing frequent opportunities for attentional reallocation, which could be small shifts within the present environment, or broadscale shifts between external and internal related thought.

Respiration Modulates Cognitive Processes

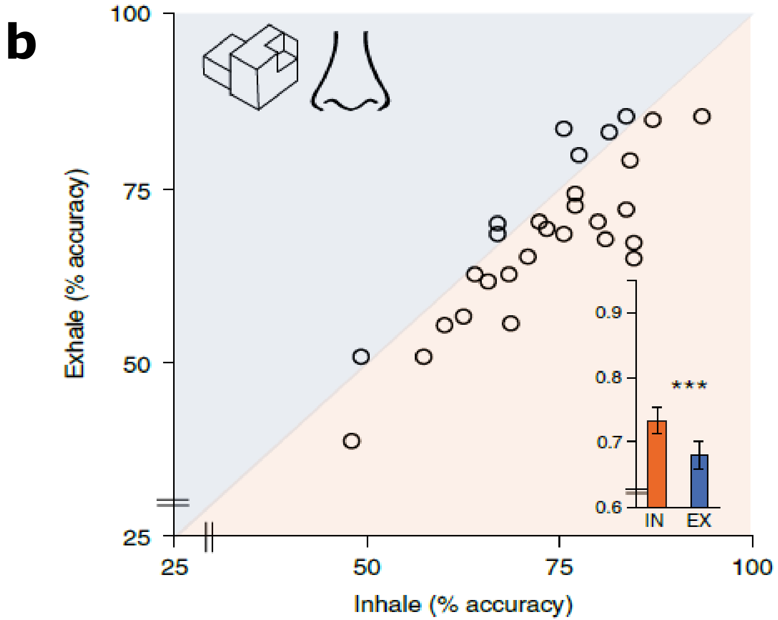
The investigation of the present thesis seeks to better understand a potential relationship between respiration and attention. A large justification for devoting a thesis to this subject is that there has been a dearth of investigation seeking to probe this linkage. Instead, recent research has focused on how respiration interacts with specific cognitive processes. In light of the previous discussion, and to make a clear distinction here, if attention is the spotlight, then specific cognitive processes can be thought of as the content in the spotlight (and all relevant informational processing). A discussion of these recent findings regarding respiratory interactions with cognitive processes can form the basis for a subsequent discussion regarding respiration and attention.

In a number of studies spanning many sensory-cognitive domains, it has been seen that the respiratory phase, e.g., inhalation or exhalation, has a significant impact on task performance or perceptual sensitivity. To give a few examples, Zelano et al., (2016) reported that participants were quicker at correctly responding in an emotion discrimination task when images appeared during inhalation (Figure I.1a). In the same study, participants had a higher accuracy in a memory retrieval task when the object image was both presented, and recalled, during inhalation. Perl et al., (2019) found that participants had higher accuracy in a visuospatial task when trials were initiated on an inhalation (Figure I.1b). Grund et al., (2022) found that participants had greater sensitivity to near-threshold electric stimulations when they were presented during exhalation. Further examples of respiratory-phase modulation of cognition has been seen for visual lexical memory (Huijbers et al., 2014), visual perception (Flexman et al., 1974; Kluger et al., 2021), memory retrieval again (Nakamura et al., 2018), and a study including tasks from six different sensory-cognitive domains (Johannknecht & Kayser, 2022).

These findings bear resemblance to the prior discussion of theta phase-dependent modulation of visual detection (Fiebelkorn & Kastner, 2019); there appears to be respiratory phases that are more or less conducive to cognitive processing, probably in a context specific manner. Rather than coincidental, domain-specific quirks, the wide ranging nature of these findings seem to suggest that respiration shapes the dynamics of information processing in the brain in a fundamental way, and indeed this has been proposed multiple times in recent years (Allen et al., 2023; Boyadzhieva & Kayhan, 2021; Brændholt et al., 2023; Folschweiller & Sauer, 2023; Goheen et al., 2023; Heck et al., 2017, 2019; Herrero et al., 2018; Kluger & Gross, 2021; Tort, Brankačk, et al., 2018).



Zelano et al. (2016)



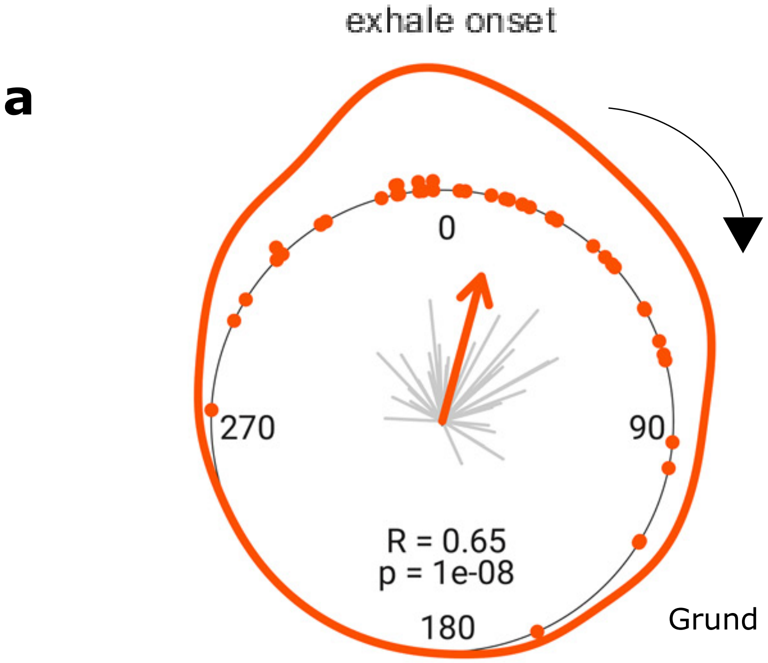
Perl et al. (2019)

Figure I.1 - Respiration modulates cognitive processes. (a) Adapted figure from Zelano et al. (2016) plotting reaction time (RT) in an emotional discrimination task (identifying fear or surprise faces), split by emotion, respiration route (nasal vs oral), and respiratory phase (inspiration/inhalation vs expiration/exhalation). Asterisks indicate significance as $p < 0.05$. Fear faces were correctly identified significantly more quickly during inhalation, and this effect was nasal route dependent. (b) Adapted figure from Perl et al. (2019) plotting accuracy in a visuospatial task where participants had to decide if drawn shapes could be real shapes. Asterisks indicate significance at $p = 0.001$. Participants had a significantly higher accuracy for trials initiated on an inhalation.

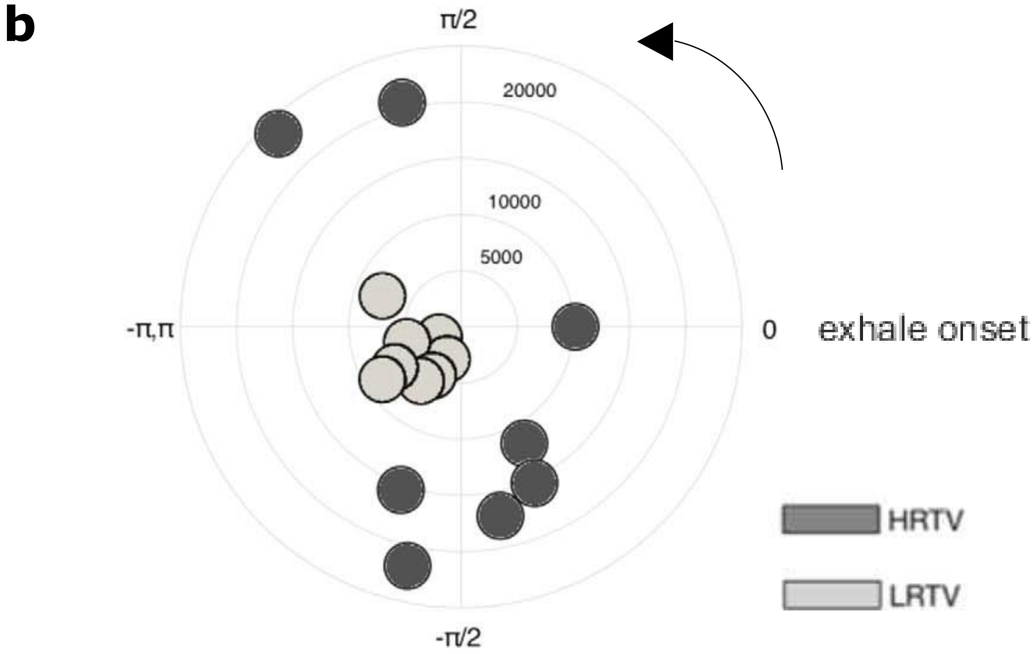
Respiration Entrains to Cognitive Demands

Not only are cognitive capabilities influenced by respiratory phase, but individuals seem to alter their respiratory rhythm so that certain phases preferentially entrain to task events. Huijbers et al., (2014) first demonstrated this effect in a visual lexical task during functional magnetic resonance imaging (fMRI), and further, showed that respiratory entrainment was stronger for subsequently remembered (versus forgotten) words. Respiratory entrainment has often been noted concomitant with findings of respiratory-phase modulation of cognition - it was present in the aforementioned studies from Perl et al. (2019), Grund et al. (2022) (Figure I.2a), and Johannknecht & Kayser (2022). Additionally, respiratory entrainment was seen to be higher for participants with relatively low reaction time variability in an auditory oddball task (Melnychuk et al., 2018) (Figure I.2b).

The relationship between respiratory entrainment and respiratory-cognitive modulation is unclear; it has not been directly tested whether one exists without the other or if causality exists between them. However, it is reasonable to assume that respiratory entrainment is of some functional importance, considering that respiratory dynamics should be significantly altered, which could feasibly come at a cost with regards to the homeostatic function of respiration. Cognitive load does indeed seem to significantly alter respiratory variability and gas exchange measures (Grassmann et al., 2016), although this has not been considered from the perspective of entrainment. The occurrence of respiratory entrainment also demonstrates that not only does respiration adapt to our internal states, but it reflects environmental demands and rhythms also, positing respiration as a sensitive mediator between our inner and outer worlds.



Grund et al. (2022)



Melnychuk et al. (2018)

Figure I.2 - Respiration entrains to cognitive demands. (a) Adapted figure from Grund et al. (2022) plotting the individuals' mean respiratory phase at the time of stimulus onset (near-threshold electrical pulse). Exhalation onset begins at 0° and the respiratory cycle continues clockwise. There was significant clustering of entrainment, from late inhalation to early exhalation. (b) Adapted figure from Melnychuk et al. (2018) plotting individuals' mean respiratory phase at the time on stimulus onset in an auditory oddball task. Exhalation onset begins at 0 radians and the respiratory cycle continues anticlockwise. The radial axis denotes reaction time variability (RTV). Participants were median split into high (HRTV) and low (LRTV) groups. LRTV participants showed significant clustering of entrainment in early inhalation.

Respiratory Modulation of Other Oscillations

The span of this respiration-cognition interplay across multiple sensory and cognitive domains implies that there is perhaps something fundamental about the role of respiration in orchestrating the rhythm of cognitive processing. There are a number of reasons why respiration makes a suitable candidate to act as a cognitive pacemaker. As aforementioned, respiration reflects, and adapts to, changing internal and external states, it can be voluntarily controlled, which facilitates altering our experience through our physiology, and additionally, it is a relatively slow physiological rhythm and therefore capable of entraining the timing of higher frequency rhythms in our body and brain.

This last point considers a role for respiration in cross-frequency coupling (Goheen et al., 2023; Klimesch, 2018; Oku, 2022; Tort, Brankačk, et al., 2018), where communication is facilitated across an organism by synchronising the timing of oscillations across multiple frequencies. Lower frequency rhythms like respiration are able to travel further in the organism and facilitate long-range communication, as opposed faster rhythms which tend to play a role in local processing (Hyafil et al., 2015).

Indeed, there has been abundant evidence reported recently that respiration modulates oscillatory activity throughout the brain and may therefore be placed at the “slower” end of an organised, oscillatory hierarchy. Cross-frequency coupling between respiration and gamma band activity was reported widespread through the cortex and limbic areas during volitional and attentive breathing (Herrero et al., 2018). At rest, respiration modulated activity in all major frequency bands and most prominently in areas overlapping with canonical neural networks (Kluger & Gross, 2021) (Figure I.3). In aforementioned studies, respiratory modulation of task relevant areas was present alongside cognitive modulation (Nakamura et al., 2022; Perl et al., 2019; Zelano et al., 2016), and a link was made between visual perceptive sensitivity and the influence of respiration on cortical excitability (Kluger et al., 2021). Respiration has also been seen to modulate oscillatory activity during sleep with implications for memory consolidation (Schreiner et al., 2023). Of high relevance to the present thesis on attention, is the finding that respiration is synchronised with, and shows significant Granger causality with, theta:beta ratio in the frontal regions, a signature of task focus (Melnychuk et al., 2021).

Collectively, these findings demonstrate that the respiratory oscillation is having a major influence on oscillatory brain activity, likely with contextual, regional and frequential specificity. Further exploration of each potential avenue of modulation is certainly warranted and should expand our understanding of how information is processed in the brain generally. Additionally, they highlight how the peripheral oscillation of respiration is orchestrating central brain activity, providing avenues for exploration from the perspective that our cognition is embodied (Varga & Heck, 2017).

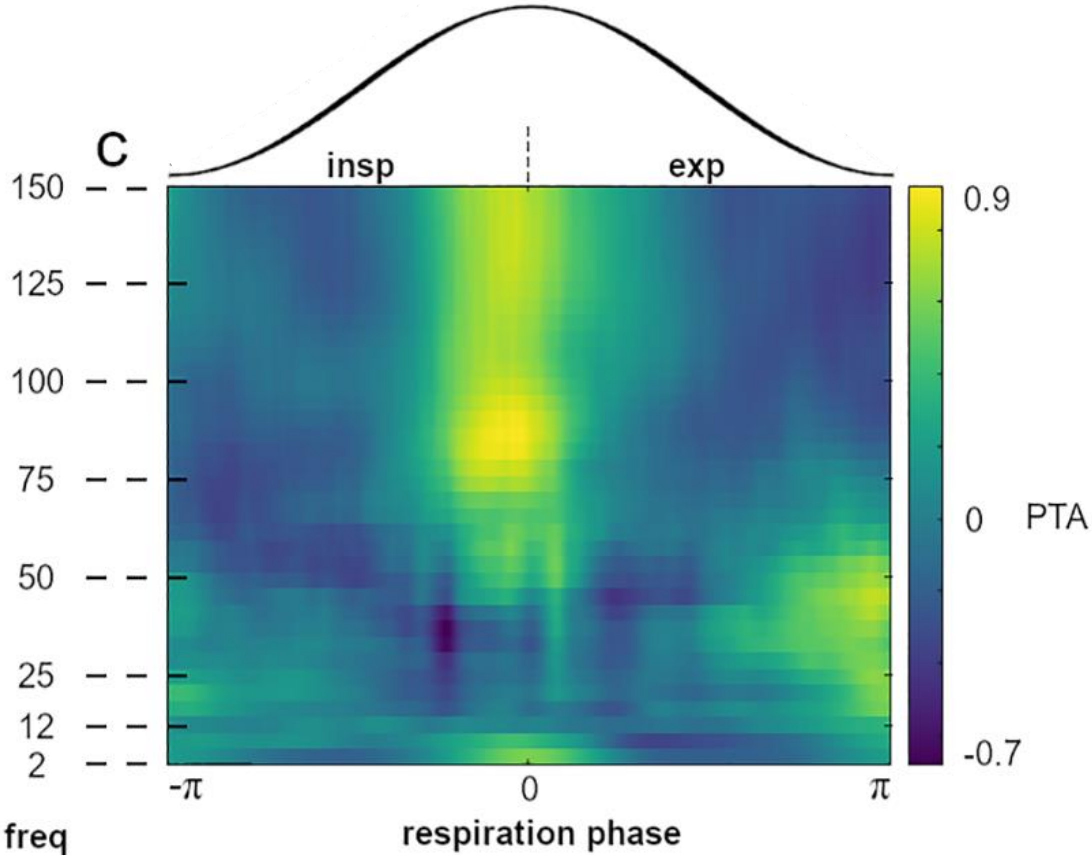


Figure I.3 - Respiration modulates oscillatory neural network activity at rest. Adapted figure from Kluger & Gross (2021) plotting the phase triggered average (PTA; calculated measure of relative amplitude for a given frequency band) across the frequencies (y axis), across the respiratory cycle (x axis). Plot represents global field power (i.e., whole brain) during quiet rest. All frequencies tested, from 2 to 150 Hz showed significant modulation (significance calculation not shown here) across the respiratory cycle. Different frequencies showed different phase-amplitude modulation patterns.

Current Theoretical Frameworks in a Respiration-Cognition Relationship

The discovery of respiratory-locked brain oscillations in rodents outside of the olfactory bulb were likely an influence for subsequent work in humans (Tort, Brankačk, et al., 2018). Respiratory-locked activity has seen in the rodent somatosensory cortex (Ito et al., 2014; Rojas-Líbano et al., 2018), visual cortex (Rojas-Líbano et al., 2018), prefrontal cortex (Biskamp et al., 2017; Karalis & Sirota, 2022; Lockmann & Tort, 2018), and hippocampus (Karalis & Sirota, 2022; Lockmann et al., 2016; Lockmann & Tort, 2018; Yanovsky et al., 2014). In particular, the observations of such activity in the prefrontal cortex and hippocampus, as well as respiration being locked to hippocampal sharp-wave ripples (Karalis & Sirota, 2022; Y. Liu et al., 2017), has lead to a particular focus of respiration shaping memory processing in the brain (Heck et al., 2019), due to these areas high involvement in memory (Buzsáki, 2015; Preston & Eichenbaum, 2013). It is worth noting that respiratory modulation of higher frequencies has been reported in the human hippocampus using intracranial electroencephalography (EEG) (Zelano et al., 2016). Additionally, respiratory-locked spindles have also been noted during sleep in humans, with consequences for memory performance (Schreiner et al., 2023), as spindles function in conjunction with sharp-wave ripples in memory consolidation (Staresina et al., 2023). Also key to this area of animal research is the emphasis on respiratory-locked gamma activity (Heck et al., 2017; Tort, Brankačk, et al., 2018), which has also been reported in humans (Herrero et al., 2018; Kluger & Gross, 2021). Firstly, because gamma oscillations are so much faster than respiratory frequency and therefore cannot be overlapping, and secondly, because of the widespread implications of gamma in higher order cognitive functions (Başar, 2013). Further, in light of the previous discussion on cross-frequency coupling, the relatively low frequency of respiration may enable it to integrate distant local areas of gamma synchrony, as suggested by Tort et al. (2018). The mechanisms underlying respiratory-gamma coupling are unknown, however, Heck et al., (2017) has suggested that the physiological properties of the cortex are sufficient to support this, evidencing this idea using their own graph theory-based simulation.

A final important consideration off the back of this area of research is whether this respiratory modulation of brain activity is nasal or oral route dependent, as it may give clues as to potential anatomical pathways. The aforementioned research in rodents is based on research from olfactory sensing and so modulation is presumed to occur via activity in the olfactory bulb (Heck et al., 2019). Research in humans, who can voluntarily choose their route of respiration implies that it may be dependant on the cognitive domain and or corresponding brain region. Arshamian et al., (2018) found enhanced olfactory memory recall when participants breathed nasally through the consolidation phase as opposed to orally. Zelano et al. (2016) found that respiratory-modulated activity in the hippocampus and amygdala was nasal route dependent, as well as performance in emotional discrimination and memory retrieval tasks. This may be explained by the direct projections from the olfactory bulb to the limbic system (Sullivan et al., 2015). Whereas Perl et al., (2019) found that performance in a visuospatial task, which does not rely on limbic system activity, was modulated by respiratory phase regardless of nasal or oral route. Effects of respiratory route may therefore depend on whether the cognitive task evokes brain activity in connective proximity to the olfactory system. It is worth noting that while this may be worth probing from an academic perspective, oral breathing is considered highly deleterious for physical and mental health and should be discouraged (Alhazmi, 2022; Fitzpatrick et al., 2003; Jefferson, 2010; Lin et al., 2022; Ribeiro et al., 2016). Additionally, experimental manipulations involving obstruction of either respiratory route is likely to cause considerable discomfort and future research should consider more non-invasive approaches such as simultaneously measuring airflow from both routes. Finally, the individuals' default respiratory route should be taken into account.

Whilst the animal research on this topic has provided interesting insights, it is also limited for a few reasons. Rodent respiration is in theta range (Tort, Ponsel, et al., 2018), which questions the validity of extrapolating findings regarding cross-frequency coupling to human brain activity. Additionally, olfactory sensing and related behaviours such as sniffing (which is considerably different to normal breathing) are of high importance to rodent exploratory behaviour, whereas in humans this is far from the case, who tend to be more visually-dominant for example (Gilad et al., 2004). Relatedly, respiration is linked to other behaviours differently in animals, such as locomotion where quadrupeds respire every stride (Bramble & Carrier, 1983). As outlined throughout this literature review, there are great advances being made in measuring respiratory-modulated behaviour and brain oscillations in humans and the need for such work in animals to understand cognition should lessen.

Relatedly, an evolutionary perspective on the origin of a sensory processing system organised by respiration considers the relative primacy of the olfactory sense and the respiratory drive behind it (Jacobs, 2021; Perl et al., 2019). Thus, this could have feasibly set an information processing template for other sensory modalities. In favour of this idea, there is a slight bias towards cognitive enhancements during inhalation vs exhalation (Kluger et al., 2021; Perl et al., 2019; Zelano et al., 2016), and across six different sensory-cognitive tasks the conclusion was that inhalation entrained to stimulus presentation whereas exhalation entrained to response (Johannknecht & Kayser, 2022). Additionally, inhalation specifically has been linked with respiratory modulated activity during tasks in the limbic system (Zelano et al., 2016) and outside the limbic system (Perl et al., 2019). Therefore, sensory information other than olfactory may also be optimally received during inhalation, with relevant brain regions primed at this respiratory phase. However, respiratory modulated brain oscillations occur throughout the respiratory cycle and are by no means restricted to inhalation (Kluger & Gross, 2021). It could be that other respiratory phases are opportune for the sensory integrating and responding. In support of this idea, spindle activity frequency associated with memory consolidation is seen to increase towards inspiratory peak (Schreiner et al., 2023), and spontaneous voluntary motor actions are associated with exhalation (Park et al., 2020, 2022), and even when they are imagined (Park et al., 2022).

Arguably, the most comprehensive attempts to provide a theoretical framework for the influence of respiration on cognitive and brain activity have been to view it within a predictive coding model of consciousness (Allen et al., 2023; Boyadzhieva & Kayhan, 2021; Brændholt et al., 2023). In brief, predictive coding models state that organisms efficiently navigate the world by generating top-down predictions regarding what they expect to experience, whilst bottom-up sensory signals provide feedback to assess errors in predictions (Den Ouden et al., 2012). Respiration provides both exteroceptive sensory information such as environmental odorants and air temperature, as well as interoceptive motor sensations from the mechanical ventilation. As aforementioned, respiration also seems to inform of when to expect stimuli through entrainment.

As suggested by Allen et al. (2023), there may be various levels through which respiration can provide prediction error information. As respiratory information ascends the cortical hierarchy, it may initially integrate with areas that seek to maintain physiological homeostasis by adjusting respiration accordingly, and then, integrate with more superficial cortical layers involved in higher order cognitive functions. It is this latter consideration that suggests how certain cognitive processes are modulated by respiratory phase.

All three papers to encroach this subject (Allen et al., 2023; Boyadzhieva & Kayhan, 2021; Brændholt et al., 2023) suggest three main pathways for respiration to modulate a predictive coding process, although this is most explicitly laid out by Brændholt et al. (2023) (Figure I.4). It is suggested that oscillatory activity in the olfactory bulb entraining to respiratory rhythm (phase-phase coupling) can modulate the rhythm of top-down predictions. Secondly, the low frequency of these rhythms enables long-range phase-amplitude coupling to higher frequency oscillations, adjusting the weighting of prediction errors in non-olfactory regions. A third and significant pathway in relation to the present thesis is the ascending modulation from the locus coeruleus (LC) and how this could adjust the weighting of the predictive processes in a global manner.

A more detailed account of the LC is discussed in the subsequent section, however, a few key details need describing here. In the **Attention** section it was described how relative degrees of LC tonic activity contributes to arousal levels and results in distinct attentional states. Through the neuromodulatory action of noradrenaline across the widespread areas that the LC innervates, it is thought that degree of LC tonic activity adjusts the neural gain of neurons. Increased neural gain means enhanced activity, whether excitatory or inhibitory, and has been shown to have effects on large-scale brain dynamics, particularly with regards to how integrated or segregated overall activity is (Eldar et al., 2013; Shine et al., 2016; Shine, Aburn, et al., 2018; Shine, 2019; Warren et al., 2016). In this way, LC activity is capable of altering the dynamics of brain functional connectivity with implications for experienced states. Crucially, the LC has been shown to have reciprocal projections with the pre-Bötzinger complex in mice (Liu et al., 2021; Yackle et al., 2017), the key inspiratory-drive nucleus. Ablation of projections from the pre-Bötzinger complex to the LC affected arousal state whilst leaving respiratory rhythm drive intact, although slower (Yackle et al., 2017), highlighting the potential role of these projections. As described subsequently, there is reason to believe that the LC receives respiratory information in humans too, with implications for attentional state (Melnychuk et al., 2018, 2021). Returning to the present focus on predictive processes, it is sufficient to say that respiratory information propagated via the LC could have broad and sustained impacts on the predictive hierarchy.

Respiratory entrainment to environmental demands as well as neural oscillations are contextualised in these models as minimising prediction error, therefore increasing the precision of predictions. Through phase-amplitude coupling to higher frequency rhythms such as gamma in relevant cognitive areas, greater prediction precision can be made about optimal respiratory phases for sensory reception and response. Through the LC pathway, neural gain can be adjusted to optimise network priming for the current task. This alignment between environment, respiration, and neural activity appears to occur without conscious awareness and thus represents an intriguing adaptive process. As emphasised by Boyadzhieva & Kayhan (2021), another reliable way to minimise prediction error would be through applying conscious attention to respiration as well as voluntarily controlling it, enhancing the weighting of this bottom-up information.

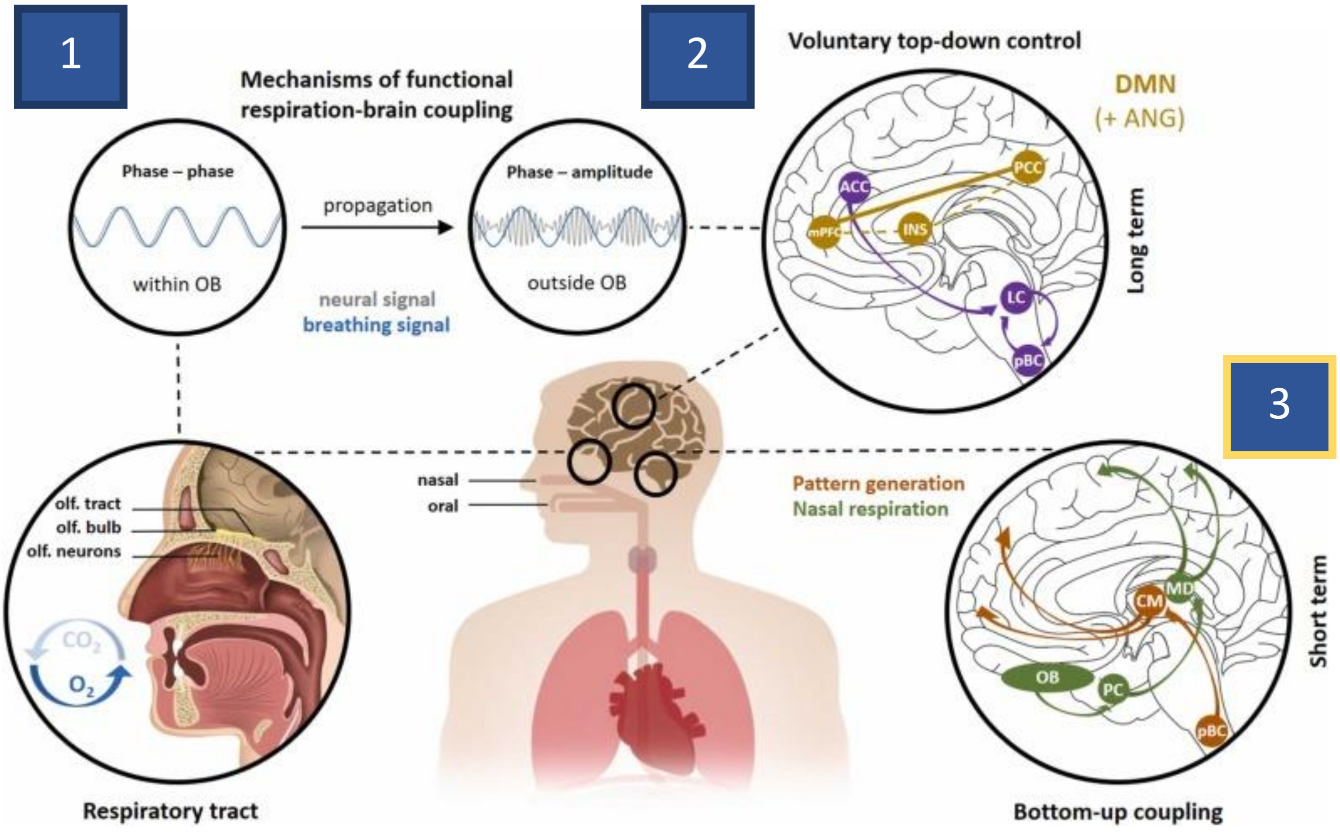


Figure I.4 - Pathways of respiratory modulation of a predictive coding process. Figure adapted from Brændholt et al., (2023) showing three pathways of potential modulation: (1) phase-phase coupling between respiration and oscillations in the olfactory bulb (OB), suggested to regulate the rhythm of top-down generated predictions. (2) phase-amplitude coupling between slow oscillations from (1) and higher frequency rhythms outside the OB, suggested to modulate the weighting of prediction error signals from sensorimotor information. (3) ascending modulation from the locus coeruleus (LC) altering neural gain and modulating the weighting of the predictive process in a global manner.

DMN = default mode network, ANG = angular cortex, ACC = anterior cingulate cortex, PCC = posterior cingulate cortex, mPFC = medial prefrontal cortex, INS = insular cortex, LC = locus coeruleus, pBC = preBötzinger complex, OB = olfactory bulb, PC = piriform cortex, CM = centromedial thalamus, MD = mediodorsal thalamus.

Respiration, Attention, and the Locus Coeruleus

Arriving at the central investigation of this thesis, it is now considered how respiration and attention may interact, with emphasis on the LC-NA system as a mediator.

On one side, it should be considered how the LC is linked with fluctuations in attention. The LC has widespread noradrenergic efferent projections, innervating areas in the brainstem, limbic system, neocortex, cerebellum and spinal cord, encompassing homeostatic, affective and cognitive regions (Szabadi, 2013). In the **Attention** section it was described how the LC tonic firing shares an inverted U-shaped relationship with task-locked LC phasic firing and complementing attentional states (Aston-Jones & Cohen, 2005b). Fluctuations in LC tonic activity appears to drive the brain in and out of task-focused states, and this can occur despite constant environmental inputs. The driving forces are thought to be fluctuations in arousal and afferents from the anterior cingulate cortex and orbitofrontal cortex which are providing information regarding ongoing task utility with respect to alternative options.

How differing levels of LC-NA activity result in attentional changes can be attributed to the effect NA has on neural gain. The action of NA on synaptic terminals is neuromodulatory, that is, it adjusts the *likelihood* of an action potential firing, through both excitatory and inhibitory means. The resultant effect on neurons is an adjustment of their neural gain. With increasing LC-NA firing comes increasing neural gain, which amplifies the neurons responsiveness to input whilst simultaneously suppressing its spontaneous activity, effectively increasing the signal to noise ratio (Servan-Schreiber et al., 1990). The timescale of this effect is relatively slow in neural terms, occurring over seconds (Thiele & Bellgrove, 2018) and can therefore be considered relevant to shifting attentional states. LC phasic firing can increase the signal to noise ratio with temporal precision in task-relevant areas, reinforcing current focuses. Changing levels of LC tonic activity can have large-scale consequences for the functional organisation of the brain, shifting broadscale attentional states.

The effect of this over the widespread areas innervated by the LC-NA system is thought to have large effects on brain network dynamics. For instance, the LC innervates areas in the frontoparietal network (Lenartowicz et al., 2013; Samuels & Szabadi, 2008a; Szabadi, 2013) which itself supports flexible cognitive control and selective attention through interactions with other cognitive brain systems (Marek & Dosenbach, 2018). Enhanced neural gain in the frontoparietal network should increase the efficacy of its interactions with other systems, facilitating sustained attention to the relevant task. Alternatively, low neural gain in the frontoparietal network would reduce its selectivity to response and potentially leave attention vulnerable to distractors (Lenartowicz et al., 2013). Activity of the LC also has effects on the

Default Mode Network (Oyarzabal et al., 2022), which itself supports internally orientated mentation (Andrews-Hanna, 2012). The relative dominance of the frontoparietal network and default mode network and the correlation between them appears to result in different attentional states. For example, a negative correlation between them, with an frontoparietal network dominance represents goal-directed, externally driven attention (Lenartowicz et al., 2013), whereas a positive correlation is thought to reflect goal-directed, internally driven attention (Christoff et al., 2009; K. C. R. Fox et al., 2015). The LC is also known to interact with activity in the salience network (T.-H. Lee et al., 2020; Neal et al., 2023), which coordinates the detection of stimuli as well as switching between frontoparietal network and default mode network dominance (Schimmelpfennig et al., 2023). The LC therefore appears capable of driving the brain in and out of different attentional states and accompanying network dynamics through changes in neural gain.

Another perspective in how LC-NA-induced changes in neural gain could account for changes in attentional state is the effect on brain integration and segregation. These ideas encompass the relative degree to which there is an activation of select clusters of local neural circuits (segregation) and how connected these circuits are with each other across longer distances (integration) (Cohen & D’Esposito, 2016; Wang et al., 2021). A variety of lines of evidence has shown how the LC-NA system alters this balance. Administration of a NA reuptake inhibitor resulted in a more segregated topology during resting state but more integrated during a cognitive task (Shine, van den Brink, et al., 2018). Increased pupil diameter (PD), a proxy for increased LC-NA-induced neural gain, was related to higher segregation in a reward-learning paradigm (Eldar et al., 2013), whereas increased PD in an N-back task positively correlated with brain integration (Shine et al., 2016). Finally, in a simulated model, increasing neural gain favoured an integrated topology (Shine, Aburn, et al., 2018). From these varied findings, it appears as though the context and the corresponding active brain regions at the time of neural gain changes is a large determinant with respect to the resultant topology of segregation or integration. However, it is suffice to say that these large-scale brain dynamic shifts should have significant consequences for fluctuating attentional states (Shine, 2019), and evidence suggests it does (Machida & Johnson, 2019; Zuberer et al., 2021).

Fluctuations in LC-NA activity that underlie these shifts in brain dynamics is typically considered to be an intra-brain process. However, it is possible that this model of attention centred around the LC neglects how this nucleus is also highly implicated in the process of respiration, and thus, the influence respiration could be having on attentional fluctuations. Research on mice has shown the preBötzinger complex, directly projects to the LC and that ablation of these neurons modulates arousal state (Yackle et al., 2017). Crucially, respiratory rhythm was unaffected which indicates how connections here may be important for modulating arousal states specifically. Another study provided evidence to suggest reciprocal projections, from the LC to the preBötzinger complex (Liu et al., 2021). Further, a considerable number of LC neurons are CO_2 sensitive in mice and rats, responding in a dose dependent manner to hypercapnia (Gargaglioni et al., 2010; Magalhães et al., 2018) and relaying this information to other key respiratory areas (Krohn et al., 2023; Lopes et al., 2016). A further respiratory input could be from pulmonary vagal afferents inputting indirectly to the LC via the nucleus solitary tract (Farrand et al., 2023; Lopes et al., 2016; Noble & Hochman, 2019). These findings implicate the LC in receiving and responding to ongoing respiratory information in animals.

For evidence for a linkage in humans, a potential modulatory effect of respiration on PD, and therefore possibly LC activity, has been investigated outside the context of a respiratory-attentional coupling. This is due to the observations that a slow oscillation of natural pupillary unrest is close in frequency to resting respiratory frequency (Bouma & Baghuis, 1971; 'THE RESPIRATORY HIPPUS', 1909). A recent review of these studies concluded that more evidence was needed, with an effect of respiratory phase modulating PD being considered "low" and depth and rate rated as "very low". Essentially, findings are mixed, and more direct testing and experiments including respiratory manipulations are warranted. Since this review was published, such a direct test with a breathing manipulation did show a remarkably strong effect of respiratory depth on modulating PD, and they discuss implications for the arousal system (Kluger et al., 2023, preprint).

Therefore, the LC has an established role in the attentional system and is highly implicated in the respiratory system and could therefore be capable of mediating between the two. In their dynamical systems model of a respiration-LC-attention coupling, Melnychuk et al., (2018) considered how the individual oscillations of respiration, and cortical regions implicated in attention, such as executive frontal regions or the default mode network, could bidirectionally influence each other via LC-NA activity. Depending on the strength of coupling between the oscillators and the nature of the individual oscillations, the result could be a stabilisation or destabilisation of attentional states (Figure I.5). From a dynamical systems perspective, an attentional state that perseveres over some period of time, e.g., task-focus or goal-directed mind wandering, is conceptualised as a ‘stable attractor’ and could conceivably co-occur when respiration, LC-NA, and cortical oscillations are synchronised. Alternatively, asynchronous activity between these oscillators could result in an unstable stable that is constantly changing. These ideas are also akin to Adaptive Gain Theory perspective of LC functioning, where intermediate LC tonic and phasic activity facilitate task exploitation (stable state), whereas high LC tonic activity results in exploration for alternative focuses (unstable state) (Figure I.5b).

Melnychuk et al. (2018) demonstrated synchronisation between fMRI blood-oxygen-level-dependent (BOLD) signal from the area of the LC and respiration, as well as between PD and respiration. In a later paper, they again showed synchronisation, as well as Granger causality, between PD and respiration. In addition, they showed the same significant analysis between respiration and frontal theta:beta ratio, as an indicator of attentional state (Melnychuk et al., 2021).

Certain predictions can be made from this model. In one direction, top-down stable attentional control applied from the frontal regions should stabilise fluctuations in LC tonic fluctuations, which could stabilise respiration. During a monotonous sustained attention task it was seen that respiratory variability decreased (Vlemincx et al., 2011, 2012a), although the involvement of the LC-NA system was not explored. In the other direction, bottom-up, stable, controlled respiration inputting to the LC could in turn stabilise activity in cortical attentional regions, facilitating sustained attention. It is intriguing to consider the reported effects of respiration entraining to task events from this perspective. Such entrainment implies a regularity in respiratory dynamics, and this effect was often reported alongside respiratory phase-specific cognitive consequences, which could feasibly arise from enhanced stability in attention. Preliminary evidence for this was demonstrated by Melnychuk et al., (2018) who showed that participants with relatively low reaction time variability in an auditory oddball task, and thus more stable performance, entrained their early inhalation period to the stimulus presentation (Figure I.2). It was during this task that they also showed synchronisation between LC and respiratory activity.

Respiratory entrainment should enhance predictability by using phases in the interoceptive signal to guide when to apply attention or not. As discussed priorly, predictive coding perspectives suggest that such alignment between respiration, environment, and cortical rhythms would be advantageous to enhance the precision of ongoing predictions (Allen et al., 2023; Boyadzhieva & Kayhan, 2021; Brændholt et al., 2023). From this dynamical systems perspective, it would be during stable attractor states where respiration, LC-NA, and attentional regions are synchronised, that respiration could be relied upon to provide predictive information. To draw a clear distinction here however, the dynamical systems model takes the perspective that these are inherently coupled oscillators, with no dependence on generated predictions.

In this way, the respiratory signal could inform of opportune windows for task focus and task inattention, aiding the balance of exploitation and exploration. This is analogous to the theta rhythms in the frontoparietal network that appear to provide opportune windows to a similar effect, though over a much less rapid timescale (Fiebelkorn & Kastner, 2019; Raposo et al., 2023).

The predictions made by this model are therefore akin to the parallels drawn by yogis between the state of respiration and the state of mind - stabilising one should stabilise the other. The LC could be a potential mediator of interacting oscillations, and the present thesis seeks to investigate evidence for this.

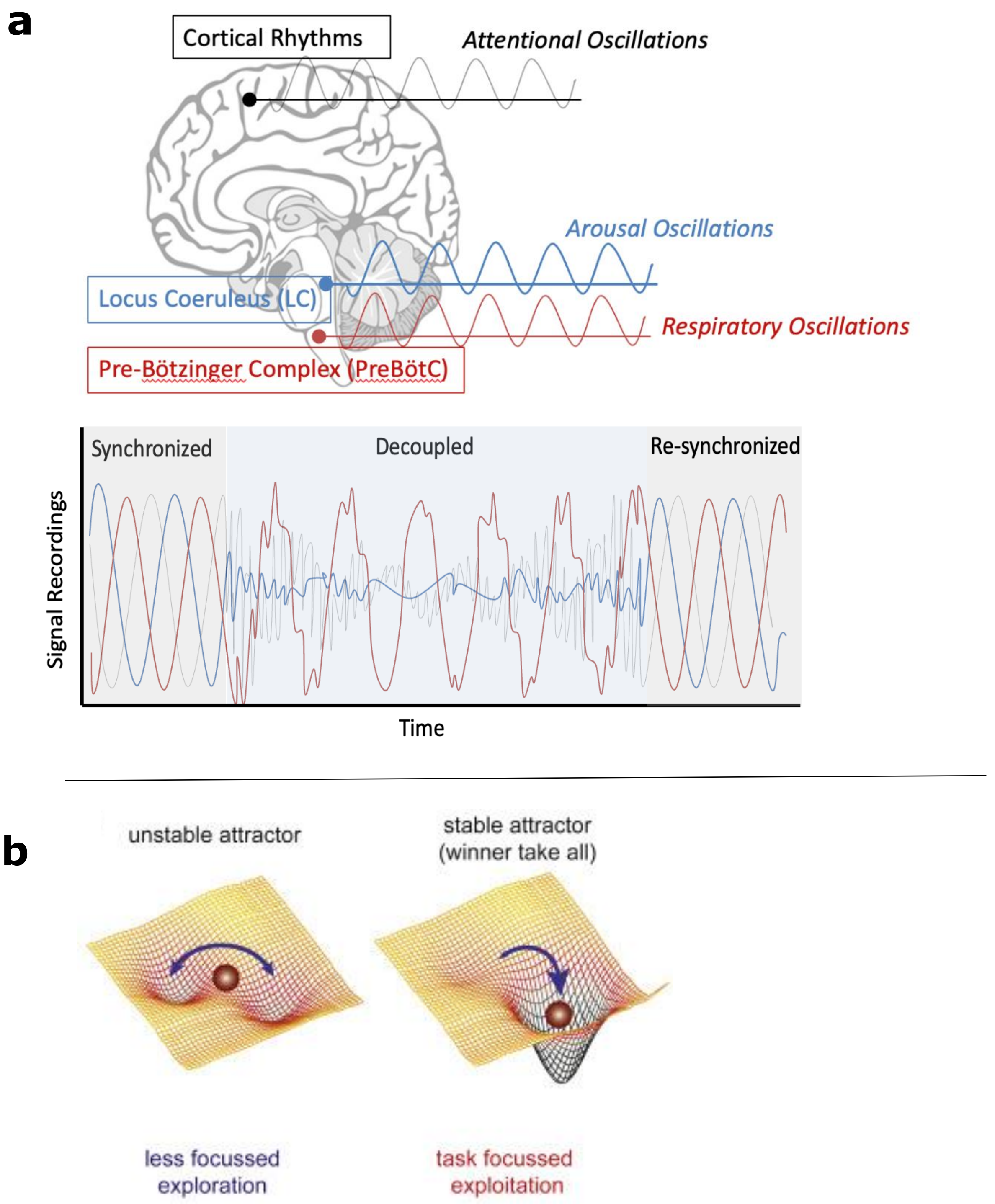


Figure I.5 - Dynamical systems perspective on respiration-locus coeruleus-attention coupling. (a) Schematic depicting synchronised and decoupled states between respiratory oscillations encoded in the the preBötzinger complex, locus coeruleus - noradrenaline oscillations, and cortical oscillations in attention relevant areas. Relative synchrony between the oscillators could entrain one another and occur with a stable attentional state (left and right sections), whereas a lack of synchronisation could destabilise attention (middle section). (b) Adapted figure from Thiele & Bellgrove (2018) for another representation of stable and unstable attentional states from a dynamical systems perspective. Exploring for alternative options for focus (left) could be thought of as attentional focus (the ball) posited between basins of attractors and thus represents a relatively unstable state. Exploitation of a particular focus (right) is when attentional focus is maintained stably in a basin of attractor.

Effects of Slow-Paced Breathing

One key prediction from the respiration-LC-attention model is that slow paced breathing (SPB) would be conducive to stable inter-dynamics with LC and attention. SPB is also the central tool used in meditative practices that seek to enhance sustained attention, and a well reported effect is that long-term meditators have a lower resting respiration rate (Karunarathne et al., 2023; Wielgosz et al., 2016). However, research for an effect of SPB on attention or even cognitive abilities more widely is surprisingly sparse. Instead, it has largely been investigated with respect to cardiovascular effects and emotional regulation (Russo et al., 2017; Shao et al., 2024; Zaccaro et al., 2018).

From the cardiovascular perspective, SPB has received a lot of attention due to the highly intriguing effects on heart rate variability. In an effect termed respiratory sinus arrhythmia, inhalation causes the heart rate to increase and exhalation drives decreases. SPB at around 6 breaths per minutes, or 0.1 Hz, causes a resonant effect in respiratory sinus arrhythmia due to the fact that the baroreflex, which responds to changing blood pressure by altering heart rate, functions with a delay of 0.1 Hz itself. Therefore, changes in heart rate are compounded by both effects occurring in harmony and there are large changes in heart rate variability (Lehrer & Gevirtz, 2014). Heart rate variability is considered a good indicator of adaptability to changing states, and is a possible biomarker for physiological and psychological wellbeing (Beauchaine &

Thayer, 2015; Grippo, 2017; Mather & Thayer, 2018; Taralov et al., 2015; Thayer et al., 2012). Heart rate variability biofeedback involves enhancing heart rate variability through SPB whilst viewing a heart rate monitor to precisely target an individual’s resonant frequency, and is found to have beneficial effects on physical, emotional, and cognitive measures (Lehrer et al., 2020; Tinello et al., 2022).

The psychological effects of SPB have been summarised by reviews to include increased relaxation and decreased symptoms of anxiety and depression (Zaccaro et al., 2018), decreased stress (Fincham et al., 2023), and a (marginal) reduction of negative emotions (Shao et al., 2024), and impressively, occur from a single session. These effects have been largely attributed to actions on the cardiovascular system as well as parasympathetic nervous system dominance via activating the vagus nerve (Noble & Hochman, 2019; Russo et al., 2017; Zaccaro et al., 2018). However, there has also been a recognition of cortical activity modulation via the nasal respiration and entrainment of the olfactory bulb (Juventin et al., 2023; Zaccaro et al., 2018), as well as the LC (Noble & Hochman, 2019).

A few studies have directly tested the effect of SPB on cognitive outcomes, closely linked with attention. A single session of SPB had positive effects on cognitive functions and retaining newly learnt cognitive skills in elderly adults (Lee et al., 2023). Hoffmann et al. (2019) had participants perform 15 min of SPB prior to a flanker task to test effects of error monitoring. The SPB group exhibited similar performance to the control group (spontaneously breathing), but a significantly greater neural signature of error monitoring following task errors which is indicative of greater task focus. Laborde et al., (2022) reported benefits on tasks measuring inhibition, working memory and cognitive flexibility following SPB, which was interestingly *not* mediated by changes in heart rate variability. Another study found beneficial effects on working memory and task switching following SPB (Bonomini et al., 2020). However, these studies considered a pre- post-SPB intervention effect, and may well be attributable to enduring effects of relaxation. The prediction from the respiration-LC-attention model is most relevant to attentional changes *during* respiratory slowing, as synchronisation potentially occurs between the oscillators. Only one study has attempted to implement a SPB intervention during a task. D’Agostini et al. (2022) had participants perform 0.1 Hz or 0.2 Hz paced breathing during a predictive learning task to test for an effect on reversal learning. Participants did successfully maintain the paced breathing rhythms during the task, demonstrating the feasibility of doing so. The authors did not find a significant effect on reversal learning between the two groups.

It is worth noting that almost every study cited in this section did not isolate the rate of respiration, with confounds including manipulations of the depth and inhale to exhale ratio. Future research should attempt to investigate the relative contributions of each dynamic on cognition. With regards to effects on the LC, it may depend on the respiratory input pathway. Information from the preBötzinger complex or fluctuating CO_2 may more reliably be encoding respiratory rate, whereas pulmonary stretch receptors would relay depth information via the vagus nerve. This may be most easily untangled through testing effects of respiratory rate and depth on PD (Schaefer et al., 2023).

There are two more studies worthy of mention here. Firstly, an EEG study testing inter-breath phase coherence found that there was a regular reduction in phase coherence within alpha frequency range during late inhalation in participants breathing at 0.125 Hz. No such significant changes were seen in the group breathing at 0.25 Hz, and thus, it seems that slower respiration has a specific effect on organising the phase dynamics in alpha band. This has potential implications for attention since alpha is predictive of subsequent stimulus detection (e.g. Mathewson et al., 2009). Secondly, in quite a remarkable study, Min et al., (2023) explored whether heart rate variability biofeedback (~ 0.1 Hz) breathing could reduce biomarkers of Alzheimer's Disease through increasing heart rate variability. They found that SPB did indeed significantly reduce amyloid beta and tau levels after 5 weeks of 20 min sessions. Interestingly, some of the differences here were associated with changing levels of noradrenergic activity, which suggests that long-term SPB interventions could alter LC-NA, and consequently, attentional dynamics.

Age-Related LC and Respiratory Degradation

Empirical Chapter 2 in the present thesis investigated respiratory and attentional measures in younger and older adults, and thus some background is warranted here.

Older adults exhibit signs of cognitive decline, some of which can be attributed to LC degradation (Calarco et al., 2022; Hämmerer et al., 2018; Mather & Harley, 2016). A seemingly paradoxical finding however, is that older adults outperform younger adults in sustained attention tasks, exhibiting higher accuracy, less errors (Vallesi et al., 2021), and less mind wandering (Moran et al., 2021; Robison et al., 2022). However, the conclusion from these studies is that older adults choose a more careful strategy, maintaining vigilance to mitigate potentially disastrous repercussions from allowing the mind to wander due to their relatively weaker cognitive abilities. In light of the LC degradation findings, this can be viewed as a lesser ability for the LC to facilitate cognitive flexibility. Older adults maintain an exploitative, task focused strategy instead of fluctuating between attentional states (Moran et al., 2021).

The respiratory system also deteriorates with age, with a decrease in respiratory muscle strength, decreased respiratory system compliance, and an increase in alveolar dead space, and an overall loss of reactivity to harmful respiratory events such as hypoxia and hypercapnia (Lee et al., 2016; Sharma & Goodwin, 2006). Respiration rate is thought to be slightly higher in elderly adults (McFadden et al., 1982; Rodríguez-Molinero et al., 2013).

No studies to date have investigated respiratory modulation of cognition, or brain oscillations, or respiratory-task entrainment in older adult populations. From the respiration-LC-attention coupling perspective, one could predict that the loss in integrity of both the LC attentional and respiratory systems may be concomitant with a loss in communication efficacy between them. Thus, it may be less likely that the respiratory and attentional systems entrain each other into synchrony. Alternatively, in the face of cognitive decline, perhaps the peripheral signal of respiration provides an alternative means to inform the individual about changes in the environment. A counter argument to this has been made, that older adults tend to prioritise visual processing over bodily sensations when informing decisions, concluding that older adults' cognition is 'less embodied' (Costello & Bloesch, 2017). Further, interoceptive accuracy appears to be weaker in older versus younger adults (Bruni, 2023; Ulus & Aisenberg-Shafran, 2022), although it is still positively correlated to cognition (Haustein et al., 2023). However, it is not clear whether interoception plays a role in respiratory modulations of cognition.

Interestingly, older adults showed a greater effect than younger adults for deep, slow breathing enhancing a measure of parasympathetic activity (Magnon et al., 2021). Therefore, it is possible that manipulations of the breath could result in more profound alterations in psycho-physiological states than younger adults. The authors view the findings through the perspective of vagus nerve functioning, which is a possible route through which respiration can communicate with the LC.

Sighs as a Respiratory Resetter

The prior discussion considers a continuous interaction that the respiratory rhythm could be having with the arousal and attentional systems. Spontaneous respiration also contains respiratory events called sighs, which are experimentally defined as having twice the volume of typical respiration (Perez-Padilla et al., 1983; Vlemincx, Van Diest, et al., 2010). The frequency of their occurrence is context dependent, but they are thought to occur approximately every few minutes (Wuyts et al., 2011).

A large body of research into sighs has been done by Vlemincx and colleagues who formalised a “resetter hypothesis” to explain their role (Severs et al., 2022; Vlemincx, Van Diest, et al., 2010; Vlemincx et al., 2022). They suggest that should respiratory variability, in rate or volume, fall outside of an ideal range, then a sigh acts to reset the variability. The “ideal range” of variability is that which facilitates the vital gas exchange function of respiration but contains sufficient variation to enable adaptability to changing states. In support of this hypothesis, tasks which caused respiratory variability to fall relatively low or high, were associated with an increased sigh frequency (Vlemincx et al., 2011, 2012a). And an analysis of variability before and after sighs also showed that variability is indeed reset (Vlemincx, Van Diest, et al., 2010).

From a comprehensive review of the research into physiological (Severs et al., 2022) and psychological (Vlemincx et al., 2022) aspects of sighs, it is more broadly suggested that sighs facilitate transitions between states. Transitions between states of arousal are implicated from both perspectives. It has been observed that sighs occur near to arousal behaviours during sleep (Perez-Padilla et al., 1983; Ramirez et al., 2013), and that images invoking high arousal, negative affect, and stress, increase sigh frequency and induce feelings of relief (Vlemincx et al., 2015). In addition, presumably there is some overlap between respiratory variability and arousal, where contexts engaging a limited set of cognitive processes in a monotonous manner over time, should decrease respiratory variability and arousal. Similarly, contexts involving rapidly changing components in a challenging manner should increase respiratory variability and arousal.

Of high relevance to the present thesis and further implicating sighs in the arousal system, is evidence from a mouse study demonstrating that sighs were NA dependent (Viemari et al., 2013). This raises the intriguing possibility that changes in the NA-related arousal level could induce sigh behaviour in an effort to reset it and facilitate transitions between arousal states. However, a link between the LC-NA system and sighs has not been drawn in humans.

If sighs interact with NA levels, this also has attentional implications considering the above discussion on the role the LC plays in arousal and attention. Although sighs have been investigated during attention tasks, it has not been investigated whether sighs influence task-derived attentional markers. Whereas the prior discussion regarding respiration on attention considers a continuous cyclic modulation, an effect of sighs might instead be associated with periodic large shifts in attention.

Outstanding Questions Addressed in this Thesis

The present thesis contains three experimental chapters that sought to enhance current understanding of how respiration and attention interact, particularly from the perspective of a coupling relationship via the LC-NA system.

In Empirical Chapter 1, a novel task will be presented to act as both a 'slow paced breathing guide with changing rates' and a 'continuous sustained attention test'. The primary aim of this study is to directly test a prediction from the respiration-LC-attention coupling model. Namely, that lowering the frequency of respiration, increases stability of attention over time, and that this is seen concomitant with a stabilisation of PD, implicating the LC-NA system in this effect. Surprisingly, this behavioural prediction has not been directly tested even outside of said model and is certainly warranted. Further, only one study has implemented slow paced breathing during a cognitive task and corroborating the feasibility of doing so should open further avenues of research. An effect for a modulatory effect of respiratory rate on PD has been rated as “very low” by a recent review (Schaefer et al., 2023), however the proposed experiment would be the most direct test of this to date.

In Empirical Chapter 2, a paradigm was utilised that previously showed differences in attentional strategy between younger and older adults, despite otherwise comparable performance. This permits an investigation into how a respiration-attention coupling could differ as a function of attention engagement. Firstly, differences in respiratory-task entrainment between the groups will be assessed to elucidate for the first time a potential contributing factor to inter-individual differences in the degree of entrainment. Further, advancing on previous work that has typically taken a binary “inhalation/exhalation” perspective for analysis of cognitive differences, the respiratory cycle will be characterised by analysing how attentional measures change over smaller phase windows. Attention measures will comprise of behavioural (reaction time) and physiological (EEG and PD) signatures, as well as thought probe-derived experiential task focus. This will be the first investigation of a respiratory modulation of subjective state. Additionally, the assessment of attentional signatures over the respiratory cycle will be contextualised relative to any entrainment phase observed, and thus, attempting to bridge the gap between these often disparately reported effects.

Empirical Chapter 3 utilises data acquired primarily for Empirical Chapters 1 and 2 to assess sigh behaviour. Here, the relationship between sighs and respiratory variability will be assessed to corroborate previous findings of a link. Additionally, it will be tested whether the attributed role of sighs to transition between states can be applied to arousal. It will be the first test of an impact of sighs on task performance, on subjective focus, and finally, a linkage between NA levels and sighs in humans, assayed through PD.

Empirical Chapter 1

Introduction

The breath is a central tool utilised by yogis and meditators of other faiths to stabilise attention. Within the 8 limbs of yoga the 4th limb is ‘Pranayama’ or ‘breath suspension/regulation’, and it is a key preparation for the 6th limb, ‘Dharana’ or ‘concentration’. (Yoga Sutras of Patanjali, circa 200 BCE). A core aspect of the sutras for Pranayama is the word “vichchhedah”, meaning “slowing/braking of the force behind”. There is a parallel drawn here between slowing the breath and slowing the fluctuations of the mind.

Despite this ancient and widely held practice, a link between slow respiration and stable attention has been remarkably understudied in contemporary Western science. Research on ‘slow paced breathing’ (<10 breaths/min) has largely focused on the reliably induced mental relaxation and improved emotional regulation, which are thought to be mediated via vagal nerve activity and changes in heart rate variability (Zaccaro et al., 2018). These pathways may provide an indirect mechanism for facilitating stable attention through relaxation; however, the yogic texts are clear in the directness of this relationship, and recent neuroscientific evidence suggests likewise.

A surge of interest in respiration within cognitive neuroscience has shown that in humans, respiration modulates electroencephalography (EEG) (Herrero et al., 2018; Perl et al., 2019; Zelano et al., 2016), and magnetoencephalography (MEG) (Kluger & Gross, 2021) activity and further, respiratory phase (i.e. inhale-exhale) modulates task performance (Johannknecht & Kayser, 2022; Nakamura et al., 2022; Perl et al., 2019; Zelano et al., 2016) and perception (Flexman et al., 1974; Grund et al., 2022; Kluger et al., 2021) across a range of cognitive domains. In these studies, there was no breath intervention and these effects, along with respiratory entrainment to task events in some cases, were present from a single session. Thus, these findings appear to represent an innate quality of respiration and its interaction with brain and mind.

This work, as well as prior work in rodents (Tort, Brankačk, et al., 2018), has led to theories that posit the breath as a low frequency 'pacemaker rhythm' that can shape the rhythm of information processing in the brain, possibly in part due to the evolutionary and developmental primacy of the olfactory sense and the breath that drives it (Heck et al., 2017; Perl et al., 2019). If respiration does indeed significantly and continuously influence the pace of cognitive rhythms, it follows that slowing down respiration would slow down fluctuations in attentional state.

The first research group to formally propose a mechanism for this link came from Melnychuk et al., (2018) who posit the locus coeruleus - noradrenaline (LC-NA) system as a key nexus that could facilitate coupling between respiration and attention. Changes in attentional state over time are concomitant to the activity of functional networks, for example, there is thought to be an antagonistic relationship between the goal-driven, externally focused nature of the dorsal attentional network, and the mind wandering, introspective-related default mode network (Fox et al., 2015; Fox et al., 2005). Melnychuk et al.’s model extends this idea of intra-cortical competition driving attentional changes by proposing that respiration is having an additional influence, from the periphery, through the LC.

Research on mice has shown that a key inspiratory driving nucleus, the preBötzinger complex, directly projects to the LC and that ablation of these neurons modulates arousal state (Yackle et al., 2017). Further, a considerable number of LC neurons are CO_2 sensitive in mice and rats, responding in a dose dependent manner to hypercapnia (Gargaglioni et al., 2010) and relaying this information to other key respiratory areas (Krohn et al., 2023; Lopes et al., 2016).

With respect to attention, the LC-NA system has been central to a seminal model by Aston-Jones and Cohen that considers the widespread connectivity and modulatory properties of the LC-NA system (Samuels

& Szabadi, 2008b) of being able to facilitate the allocation of attention by determining the neural gain of attentional networks (Aston-Jones & Cohen, 2005b, 2005a). The LC displays two distinct firing modes: i) tonic mode, where baseline NA firing is high, cortical neural gain is high, and network activation and attentional state are distributed, and ii) phasic mode, where NA firing is task-locked, neural gain is low, task specific networks are active, and attention is selective. A fluctuating dominance in these modes facilitates an optimal exploration-exploitation balance of behaviour, periodically broadening and narrowing the scope of focus. Much of this model is evidenced by animal research (Aston-Jones & Cohen, 2005b), however recent studies in humans using pupil diameter (PD) as an LC proxy measure have supported the model also (Jepma & Nieuwenhuis, 2011; P. R. Murphy et al., 2011; Regnath & Mathôt, 2021; van den Brink et al., 2016). PD is a commonly used proxy measure for LC-NA activity (Bang et al., 2023; DiNuzzo et al., 2019; Elman et al., 2017; Meissner et al., 2023; P. R. Murphy et al., 2014), however, it should be noted that this relationship is not fully defined as changes in PD also correlate to other brain areas (DiNuzzo et al., 2019; Joshi et al., 2016), and there are other neuromodulators of PD besides NA (Cazettes et al., 2021; Larsen & Waters, 2018; Reimer et al., 2016).

The dynamical systems model from Melnychuk et al. (2018) proposes that since the LC is simultaneously receiving oscillatory respiratory information, and facilitating oscillations in attentional state, modulating either respiration or top-down attentional control could influence the activity of the other. These ‘autonomous noisy oscillators’ could act coherently, pushing attention into a stable attractor state, or incoherently, destabilising attention. In the same paper, they provide evidence for such a mechanism in humans, demonstrating synchronisation between respiration and LC functional magnetic resonance imaging (fMRI) blood-oxygen-level-dependent (BOLD) activity as well as PD (Melnychuk et al., 2018). In a later study they extended this relationship to a significant synchronisation and information transfer between respiration, PD, and EEG derived frontal theta:beta ratio as an attention-related cortical measure (Melnychuk et al., 2021). However, direct tests of the model’s predictions in humans during breath manipulation are yet to be studied.

One such prediction of the model would be that reducing respiratory frequency reduces variability in LC-NA firing, which could be assayed from PD activity, and also reduces behavioural variability through stabilisation of the attentional state. Considerable work has sought to investigate whether respiration can modulate pupil activity, in the absence of attention measures. A recent review on the topic (Schaefer et al., 2023) concluded that the strength of evidence for an effect of respiratory phase on pupil dynamics was “low” and of rate and depth was “very low”. Direct tests of a link between respiration rate and pupil dynamics have so far generally sought to correlate their respective activities at rest. To our knowledge, only one study has attempted to manipulate respiration rate for a modulating effect on PD activity (Daum & Fry, 1981). They found support for such an effect, however only with 3 participants.

In the present study we sought to test the hypothesis that slow paced breathing leads to a stabilisation of attention concomitant with a reduction in PD oscillation frequency. To this end, we implemented a novel task, the Paced Auditory Cue Entrainment (PACE) task where the stimuli are both a breath guide and rhythmic response targets for monitoring stability of attention during the breath intervention. Results were compared within group for an effect of respiration frequency and to a control group that only responded to targets without breath instructions. We chose a respiratory frequency range of 0.1 – 0.15 Hz to align with the current literature on psychophysiological effects of slow paced breathing (Zaccaro et al., 2018) and the range for slow pranayama.

Comprehensively, our study questions were:

(1) Does slow paced breathing affect:

    (i) Behavioural attentional stability?
    (ii) PD oscillatory frequency?
    (ii) The phase coupling relationship between respiration and PD?

(2) Do respiratory-related PD oscillations correlate to any behavioural outcomes?

Methods

Participants

We based our required sample size on previous studies investigating a modulatory effect of respiratory rate on PD as there has been more work here than for an effect on attention. Sample sizes under 15 have shown positive findings, whereas those over 15 have been negative (Schaefer et al., 2023; their Figure 4). We aimed for 30 in the breath intervention group and 30 controls. In total, 66 participants were recruited through Trinity College Dublin communications, all students at the college, aged 18-29 years old. Inclusion criteria for the study required participants not currently experiencing respiratory illness. When asked 'How often do you pay attention to your breath in daily life?', 9 participants made comments akin to 'quite often', otherwise participants stated it was only during specific activities/scenarios, e.g., sports, anxiety, or not at all. Overall, we deemed our sample population to be largely naive to breathwork exercises, and completely naive in the breath intervention group.

The number of participants included in each analysis will be stated in each section as it depended on data quality and/or task compliance – each stage of attrition will be explained.

Protocol

Participants were given an information sheet that described the study broadly as an investigation into the physiological correlates of sustained attention. They then provided demographic information and filled in the Trait Meta-Mood Scale and the pre-task Short Stress State Questionnaire to assess trait and state psychological characteristics respectively. Before the main task, the PACE task, resting respiration rate was recorded for 3 minutes. Participants were randomly assigned to an 'instructed breath' (IB) or a control 'no instructed breath' (NIB) group for the Paced Auditory Cue Entrainment (PACE) task and wore headphones to hear the task's auditory stimuli. Volume was kept constant across participants. We attempted to keep the NIB group naive to our focus on respiration by informing them that the respiration belt was also a heart rate monitor and that the study was about 'the physiological response to periods of sustained attention'. Both groups completed the main task with the presence (IB) or absence (NIB) of breathing instructions. They then filled in the post-task Short Stress State Questionnaire and a post-task qualitative questionnaire, were debriefed, and paid €10 (TangoCard voucher) or given course credits for the hour session.

Paced Auditory Cue Entrainment (PACE) Task

The PACE task was novelly designed to be a simultaneous ‘paced breath guide with changing rates’ and a ‘sustained attention task’. See Figure 1.1 for task schematic. Created in PsychoPy, the task lasts 21 minutes where the participant hears two tones continuously alternating, one higher and one lower in pitch. There are 5 blocks: In block 1 (5 mins) the two tones alternate in a 6.5 s cycle, i.e., 3.25 s higher tone, 3.25 s lower tone, or 0.15 Hz. In block 2 (3 mins) the cycle incrementally increases in length each cycle until it reaches 9.95 s, or 0.1 Hz. Block 3 (5 mins) is a constant 0.1 Hz cycle. Block 4 (3 mins) the tone cycle decreases in length back to 0.15 Hz. Block 5 (5 mins) is a constant 0.15 Hz cycle (same as Block 1). All participants are instructed to time rhythmic mouse clicks precisely to the transition points between tones - left click for the high → low transition (HL), right click for the low → high transition (LH). The IB group was given additional instructions to breathe along with the tones so that they are inhaling with the high tone and exhaling with the low tone. They were also told to try and maintain a natural breath depth. The NIB group was given no explicit instructions regarding breath. The changes in tone cycle duration were not mentioned in the instructions and were intended to be subtle, but not necessarily sub-perceptual to the participants. During piloting, decreasing the tone cycle length to 10 s (precisely 0.1 Hz) in Block 3 appeared too salient and thus 9.95 s was chosen. In addition, a 6.5 s cycle was slightly closer to natural breathing rate than 6.67 s. It therefore should be noted that more precisely, the frequencies of interest are 0.154 and 0.10 Hz. Blocks 4 and 5 were included to ensure that any difference in outcome measures is due to an effect of tone/breath cycle rate rather than ‘time on task’.

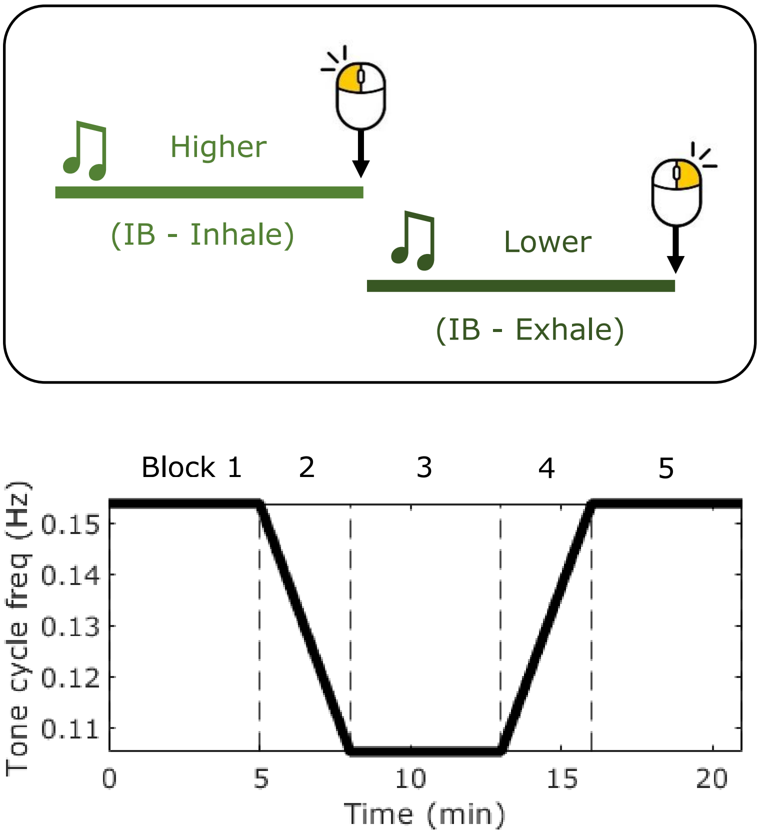


Figure 1.1 - Schematic for Paced Auditory Cue Entrainment (PACE) task. Participants heard a higher pitched tone and lower tone cycling continuously for 21 minutes. Both of which they had to rhythmically respond to with mouse clicks so that left clicks landed on the high → low transition and right on the low → high. An ‘Instructed Breathing’ (IB) group had to additionally inhale during the higher tone and exhale during the lower tone. A ‘No Instructed Breathing’ (NIB) group only responded with mouse clicks. The tone cycle frequency changed over time, starting at 0.15 Hz in block 1, slowing to 0.1 Hz in block 2, remaining at 0.1 Hz in block 3, then speeding up 0.15 Hz in block 4 and then it remained at 0.15 Hz in block 5. Thus, the rate of mouse responses and rate of respiration for IB only, changed accordingly.

Questionnaires

The Short Stress State Questionnaire (Helton, 2004) and the Trait Meta-Mood Scale (Salovey et al., 2011) and were implemented to provide state and trait measures respectively. The Short Stress State

Questionnaire has the facets of ‘Engagement’, ‘Worry’, and ‘Distress’. The Trait Meta-Mood Scale has the facets of “Clarity of feelings’, ‘Attention to feelings’, and ‘Mood Repair’. The data from these questionnaires was primarily of interest to a different study to the present one, and thus, full results are not reported for these, however a small number of significant correlations with other variables are reported. A post-task qualitative questionnaire was implemented primarily to get feedback on the PACE task and to assess the naivety of the NIB group to our study’s focus on respiration. Questions were: (1) *Were you able to easily follow along with the tones using mouse clicks?* (2) *Did you notice anything change about the tones?* (3) *What did you think the point of this study was?* (4) *How much attention did you pay to your breath during this study?* (5) *How often do you pay attention to your breath in daily life?*

PACE Task Behavioural Analysis

Reaction time mean and variability: The primary behavioural variables of interest to assess attentional stability from the PACE task are the (i) precision of click timing in relation to the tone transition time, reaction time mean (RTm), and the (ii) circular vector length of RTs (RTVL). Since the PACE task has cyclical stimuli, RTs were calculated as absolute phase angle deviations from 0 radians - the tone transition time. RTm was calculated across the task and for the primary blocks of interest, blocks 1, 3, and 5, where tone length was constant at the frequencies of interest. RTVL was represented by the vector length of RT phases - a circular statistic for variation in phase distribution (See Methods; Respiration recording and analysis; for more details).

Response Errors: As an exploratory analysis, ‘inverted responses’ (IRs) were extracted as the number of times participants clicked the incorrect mouse button with respect to the tone transition type. IRs were detected as mouse clicks at phase deviations > π/2 from tone transitions and were thus more aligned to the opposite tone transition than the expected one. We additionally considered ‘Switches’ – the count of instances when participants altered their response pattern, both correct to incorrect, and incorrect to correct.

Non-compliance to task: We also considered the number of registered clicks compared to the number of expected clicks (340 tone transitions) to use as a measure of task compliance.

Values for these analyses were extracted from the csv file generated by PsychoPy and computed using MATLAB 2022b.

Respiration Recording and Auditory-Respiratory Entrainment Analysis

Respiration was continuously measured using a SleepSense effort sensory respiratory belt (https://sleepsense.com/) placed approximately at the bottom of the sternum. The signal was recorded with a Biosemi amplifier and Actiview software (https://www.biosemi.com/), sampled at 256 Hz. In pre-processing, the signal was checked by eye for clear recordings and then low pass filtered using a zero-phase digital Butterworth filter with cutoff frequency 0.6 Hz and filter order 4. Filtered signals were then linearly detrended.

To represent the strength of respiratory entrainment to the tone stimuli, the consistency of respiratory phases occurring at the time of tone transitions was calculated: For this, the respiration signal was Hilbert transformed (‘hilbert()’; MATLAB) and phase angles were extracted (‘angle()’; MATLAB) so each sample point laid between -π and +π radians and could be represented on a circle. The resultant vector length from plotting the respiratory phases at tone transition times (‘circ_r()’; MATLAB) represents the degree of entrainment and lies between 0 (arbitrary distribution) and 1 (distributed to a singular phase angle). These auditory-respiratory vector lengths were analysed separately for HL and LH since it is known that respiratory phases differentially entrain to certain task events (See Introduction).

Additional measurements for entrainment are the mean phase angle that the resultant vector tends towards (‘circ_mean()’; MATLAB), and a test result from the Rayleigh test of non-uniformity around a circle (‘circ_rtest()’; MATLAB). Circular statics functions were used from CircStat Toolbox (Berens, 2009a). For more information on circular statistics see Cremers & Klugkist (2018).

Pupil Recording and Analysis

PD was continuously recorded using an Eyelink 1000 Plus camera and associated SR Research software, sampled at 1000 Hz. Calibration and validation of the pupil was performed once, prior to the task commencement. To process PD data, periods of eye closure due to blinking or otherwise were detected using the Eyelink algorithm ± 50 ms, were removed, and interpolated linearly. PD was then low pass filtered using a zero-phase digital Butterworth filter with cut-off frequency 4 Hz and filter order 4, and linearly detrended.

The primary analyses on PD were: (i) the power of frequency components across the task and for each block, obtained via fast Fourier transform (‘fft()’; MATLAB), (ii) spectrogram analysis to see how frequency power changed over a finer timescale and, (iv) the phase relationship with respiration (next section).

Respiratory-Pupillary Phase Coupling Analysis

Phase locking values (PLVs) and the corresponding mean phase angle differences were calculated to assess phase-phase coupling and phase offset respectively between respiration and PD. Following the aforementioned pre-processing steps for each signal, they were both bandpass filtered with a Butterworth filter of order 2, in the range of 0.01 - 0.4 Hz. This was to encompass low frequency sigh behaviour and highest respiration rate recorded for any block. Filtered signals were transformed into phase angles and the angular difference (‘angdiff()’; MATLAB) was taken between them at every sample point. The resultant vector length of plotting these angular differences represents the consistency of the phase difference between these signals over time, thus assessing 1:1 phase-phase coupling strength. The mean of these angular differences provides a measure of phase offset. Mean PLV was calculated for the task overall, for each block, and as a moving average across the task with window size 10 s and step of 2 s for a finer analysis of this relationship over time. To determine the significance of task PLVs vs chance, the actual PLVs obtained were compared against the mean of surrogate PLVs + 1.65 std. Surrogates were generated for each participant by randomly shifting the phase representation of their respiratory signal and calculating PLVs with PD 10,000 times. We additionally plotted grand average PD over the respiratory cycle for each block. This was performed by averaging PD within a moving phase window around the respiratory cycle, using window of 5° and step of 1°.

Results

Appendix 1 includes an analysis of manipulations checks and validity of the novel PACE task. Overall it was deemed that the IB group followed the respiratory guide well, the NIB group showed little respiratory entrainment to the tones and the task was generally well complied to.

(1) (i) Does SPB affect attentional stability?

RTm and RTVL

For RTm at the task level, the IB group ranged 0.06 - 0.68 rad, M = 0.24 rad ± 0.03, and the NIB group ranged 0.11 - 0.78 rad, M = 0.27 ± 0.03. For RTVL, the IB group ranged 0.94 - 99, M = 0.97 ± 0.002. NIB group ranged 0.92 – 0.985, M = 0.97 ± 0.004. See RT phases distributions in Figure 1.2.

10 NIB participants were deemed to have a high number of response rhythm errors, termed inverted responses (IRs; see next section). As this could be an indication of poor task compliance, block-wise analysis of RTm and RTVL were conducted with (IB n = 23, NIB n = 31) and without (NIB n = 21) these 10 participants. For block analyses, blocks 1 (0.15 Hz), 3 (0.1 Hz), and 5 (0.15 Hz) were compared.

Testing for differences in RTm between groups across blocks, a two-factor circular ANOVA, Harrison Kanji test was used. With NIB n = 31 there was no significant effect of block, $\chi 2(2) = 1.19$, $p = 0.31$, or group, $\chi 2(1) = 1.64$, $p = 0.21$, or interaction $\chi 2(2) = 0.07$, $p = 0.94$. The conclusions were the same with NIB n = 21: there was no significant effect of block, $\chi 2(2) = 2.13$, $p = 0.12$, or group, $\chi 2(1) = 0.92$, $p = 0.34$, or interaction $\chi 2(2) = 0.08$, $p = 0.92$ (Figure 1.2).

For RTVL, (NIB n = 31) RM-ANOVA showed a significant main effect of block, F(2) = 10.81, $p < 0.001$, with significant differences for blocks 1 vs 5 and 3 vs 5, but no main effect of group, F(1) = 0.77, p = 0.39, or interaction, F(2) = 0.21, p = 0.13. Without the 10 NIB participants (n = 21) the conclusions were the same: RM-ANOVA showed a significant main effect of block, F(2) = 15.5, $p < 0.001$, with significant differences for blocks 1 vs 5 and 3 vs 5, but no main effect of group, F(1) = 0.05, p = 0.82, or interaction, F(2) = 0.82, p = 0.45 (Figure 1.3a). RTVL was lowest in block 5 which means the highest variability since it is a vector length representing RT clustering.

RTVL differed by tone transition type as seen by RM-ANOVA: significant main effect of transition type, F(1) = 24.30, $p < 0.001$; no significant effect of group F(1) = 0.05, p = 0.82, or interaction F(1) = 1.86, p = 0.18. Looking at how LH/HL RTVL was affected across the blocks for each group in isolation, IB showed a significant main effect of block F(2) = 21.4, $p < 0.001$, and transition type F(1) = 4.41, p = 0.04, and interaction F(2) = 3.38, p = 0.04. NIB showed significant effect of block, F(2) = 6.63, p = 0.002, non-significant for transition type F(1) = 0.63, p = 0.43, and a trend for an interaction, F(2) = 2.93, p = 0.06. In both groups, LH RTVL seems to decrease steadily with each block whereas HL RTVL is comparable in blocks 1 and 3, then a sudden decrease in block 5 (Figure 1.3a).

RTm did not significantly differ by HL/LH tone transitions for IB (F(1) = 1.26, p = 0.27) or NIB (F(1) 2.83, p = 0.1).

Neither the skewness nor kurtosis of the RT distribution significantly differed by block or group.

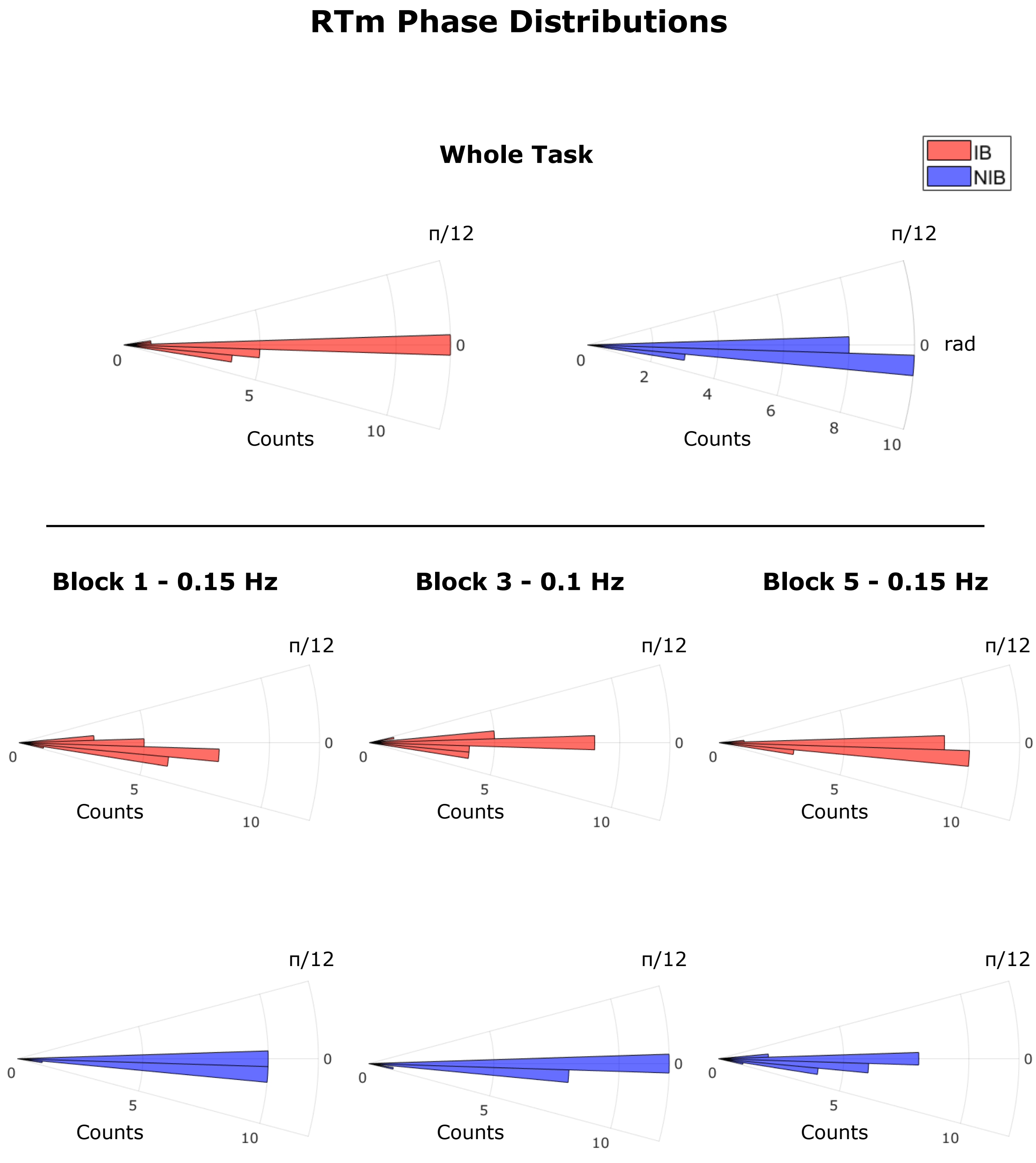


Figure 1.2 - RTm phase circular histograms showing the distributions of participants' RTm around time of tone transition, 0. Whole task (top) and by block (bottom). Angular axis ranges from -π/12 to -π/12 radians where negative values indicate early responses and positive, late. Bottom - Same analysis split by block.

Inverted Responses (IRs) and Switches

IRs represent the number of incorrect responses with respect to the correct ‘HL-left, LH-right’ rhythm. ‘Switches’ represent the counts of when the participants’ response pattern changed between correct and inverted. These were counted across all 5 blocks. NIB participants with IRs between 19% - 100%+ of expected clicks were deemed to be ‘severe’ and were excluded from the above RTm and RTVL analysis.

IB IRs ranged 0 – 11 (0 – 3.2% of expected clicks), M = 2.57 ± 0.59 (0.77% ± 0.17). NIB IRs ranged 0 – 353 (0 – 103.8%), M = 58.10 ± 16.88 (17.10% ± 4.96). RM-ANOVA showed a significant main effect of block F(4) = 2.78, p = 0.028, group F(1) = 7.99, p = 0.007, and interaction F(4) = 2.45, p = 0.047. IRs seemed to steadily rise over the blocks for IB, whereas NIB showed the highest in blocks 1 and 5 and lowest in 2 and 4 (Figure 1.3b).

IB Switches ranged 0 – 20, M = 4.04 ± 1.02, NIB ranged 0 – 63, M = 11.40 ± 2.30. RM-ANOVA showed a significant main effect of block F(4) = 5.76, p = 0.004, and group F(1) = 7.42, p = 0.009, but no interaction F(4) = 1.61, p = 0.19. IB Switches were higher in blocks 4 and 5 whereas NIB Switches were higher in blocks 3 and 5 (Figure 1.3b).

There were significant negative correlations between IRs and auditory-respiratory vector lengths in the IB group (LH: r(42) = -0.44, p = 0.03;

HL: $r(42) = -0.56$, $p = 0.005$), as well as Switches with HL ($r(42) = -0.53$, $p = 0.009$). This implies that the greater the auditory-respiratory entrainment, the fewer lapses.

There was additionally a highly significant correlation in the IB group for the Trait Meta-Mood Scale-derived ‘Mood Repair’ facet, with both IRs, $r(21) = -0.66$, $p < 0.001$, and Switches, $r(21) = -0.54$, $p = 0.008$. Both correlations survive Bonferroni multiple comparison correction at $p < 0.017$. No such correlation was significant in the NIB group, including or excluding the 10 ‘severe’ IRs participants.

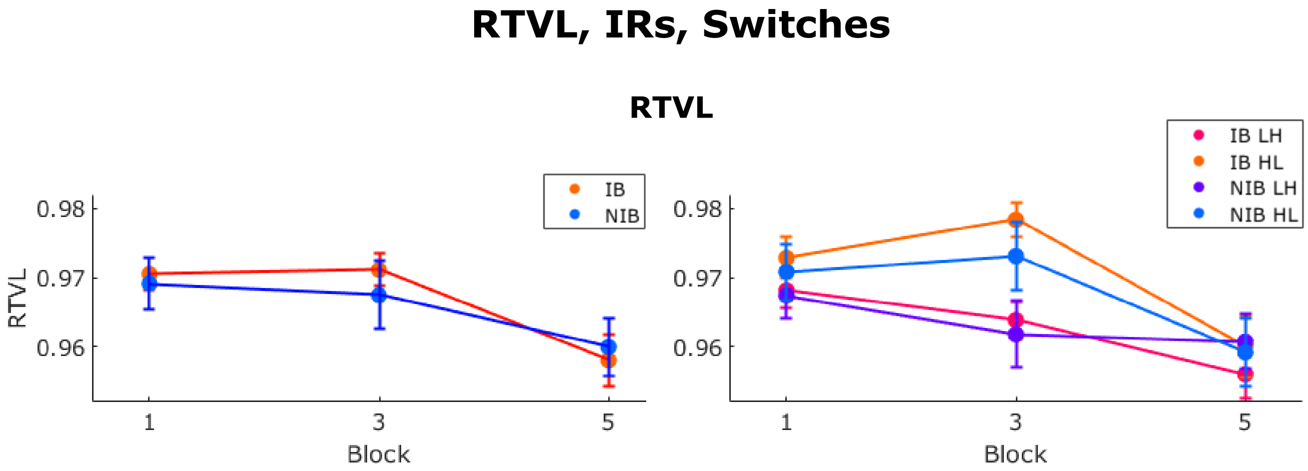


Figure 1.3a - Left: RTVL across blocks 1, 3 and 5. Right: Same split by tone transition type.

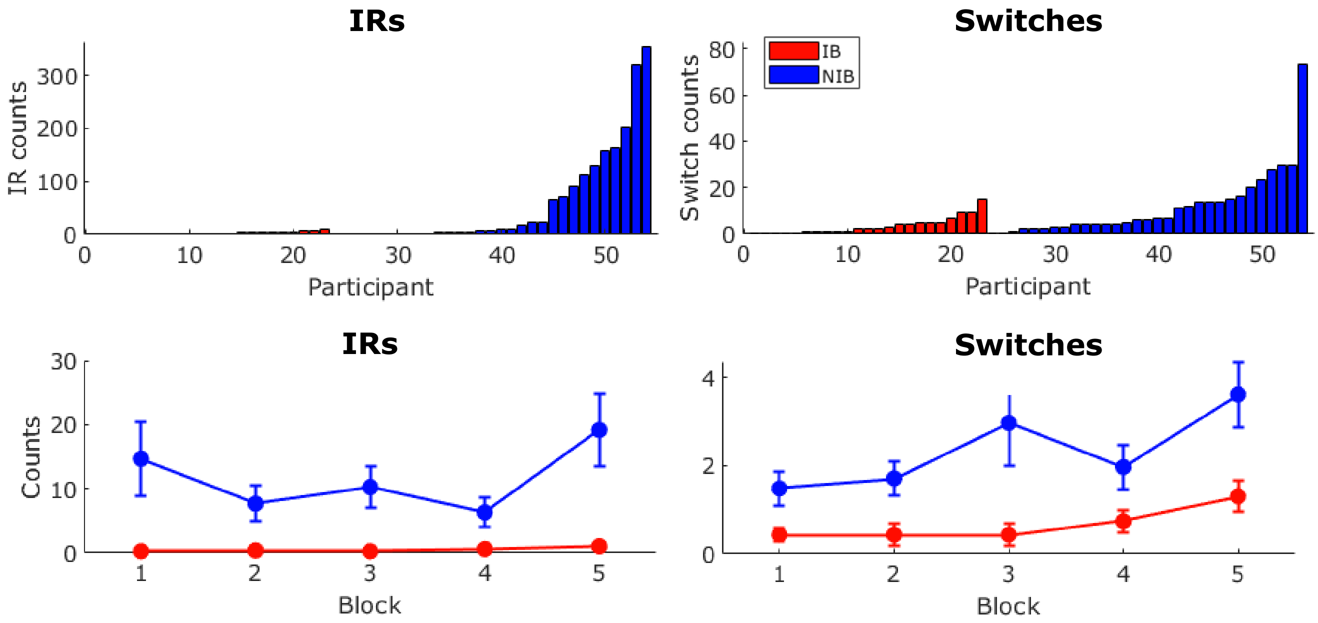


Figure 1.3b - Top: Total counts of IR and Switches. Bottom: IR and Switches across blocks, error bars indicate SEM.

(1) (ii) Does SPB affect PD oscillatory frequency?

PD Power Spectra

To investigate the presence of a respiratory frequency component in the PD oscillations, we considered the power of PD frequencies at the guided respiratory frequencies of interest, 0.1 Hz and 0.15 Hz. For the subsequent analyses involving PD, one participant from the NIB group was removed due to poor quality PD data (IB n = 23, NIB n = 20).

The grand average power spectrum across the whole task for each group, shown in Figure 1.4, shows clear peaks at 0.1 Hz and 0.15 Hz in the IB group which are absent in the NIB group. t-tests at the peaks of interest showed significant differences: 0.1 Hz - $t(41) = 2.69$, $p = 0.01$; 0.15 Hz – $t(41) = 3.24$, $p = 0.02$.

We also looked at power spectra for each of blocks 1, 3 and 5 to evidence further that these peaks are related to the respiratory frequency of that block (Figure 1.4). t-tests at the peaks of interest showed significant differences: Block 1 0.15 Hz – $t(41) = 2.28$, $p = 0.03$; Block 3 0.1 Hz – $t(41) = 2.55$, $p = 0.015$; Block 5 0.15 Hz – $t(41) = 3.37$, $p = 0.002$.

Also present in the spectra for both groups are peaks at 0.3 Hz in blocks 1 and 5, and 0.2 Hz in block 3. Means comparison tests show no significant difference between the power of these peaks in each group at the task or block level (all $p > 0.2$). These shared peaks could possibly be induced by the auditory stimulus and will also be considered in the section correlating PD frequency power with behavioural variables.

Respiration and PD Spectrograms

To further evidence that the changing rate of respiration correlated to a shift in dominant PD frequencies within the same range, spectrograms for both were plotted across the task (Figure 1.5). For the IB group the respiration plot follows the tone cycle closely, however, block 5 appears to have reduced power at 0.15 Hz vs block 1 and there is some additional lower frequency activity. The PD frequency power approximately follows respiration for IB. Block 1 is dominated by 0.15 Hz, in block 2 the 0.15 Hz component progressively decreases to 0.1 Hz, during block 3 there is a dominant 0.1 Hz component, and then the pattern is less clear during blocks 4 and 5 where there is significant power throughout the 0.1 - 0.15 Hz range in a variable manner. The NIB group do not show a clear dominance of respiratory frequencies, however, there does appear to be some subtle but consistent activity at 0.15 Hz during block 1. The dominant shifts in PD for NIB are within the 0.2 - 0.3 Hz range but broadly showing a similar pattern to the IB changes - starting at 0.3 Hz, shifting to 0.2 Hz, and back to 0.3 Hz. A spectrogram plotted of the difference in PD frequency power between the groups (IB minus NIB; Figure 1.5) shows increased power in the 0.1 – 0.15 Hz range, predominantly in blocks 2 and 3.

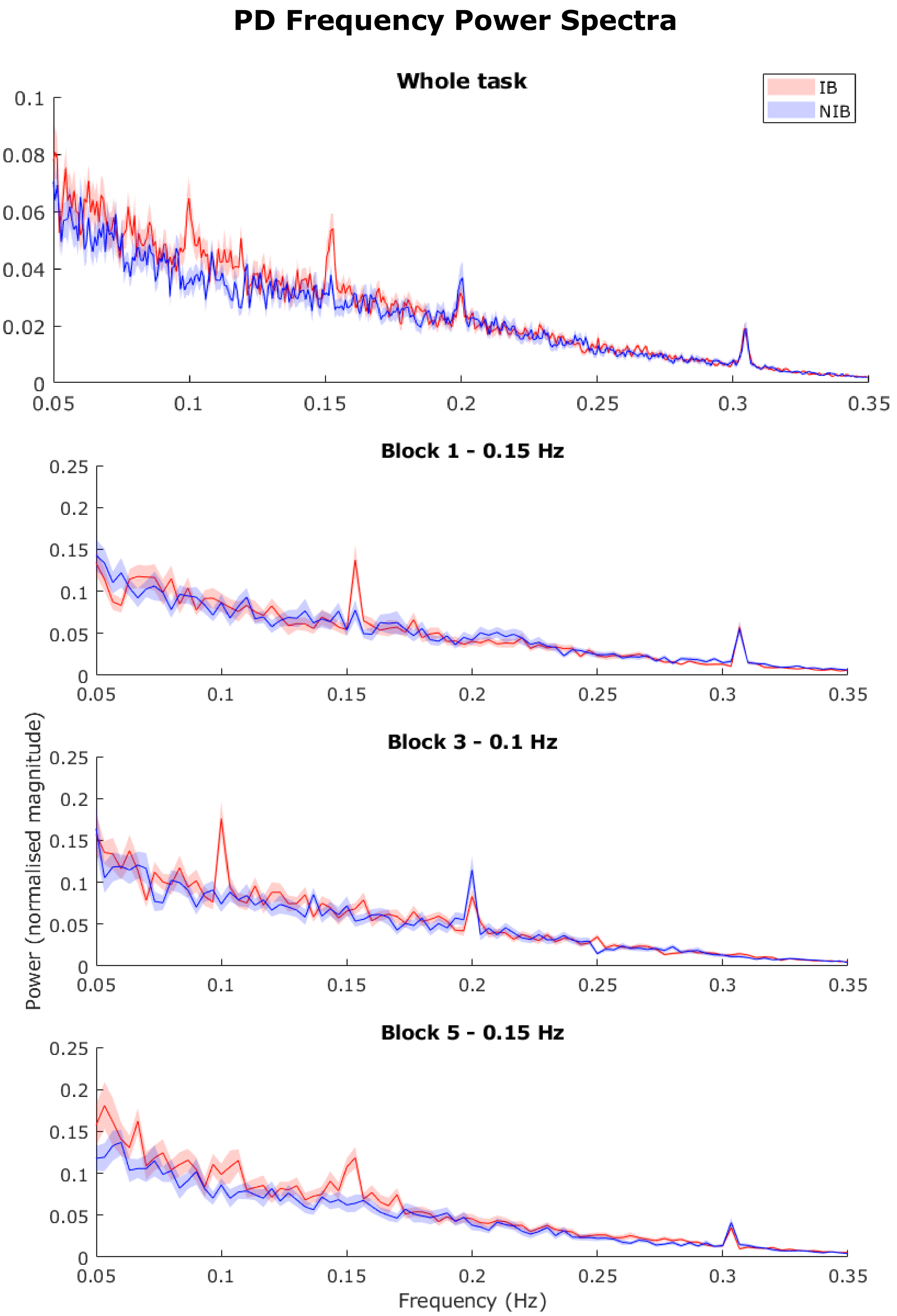


Figure 1.4 - Pupil diameter power spectrum across the whole task (top) and split by block (bottom). Shaded areas represent SEM. Asterisks indicate frequencies where power significant differs between groups ($p < 0.02$).

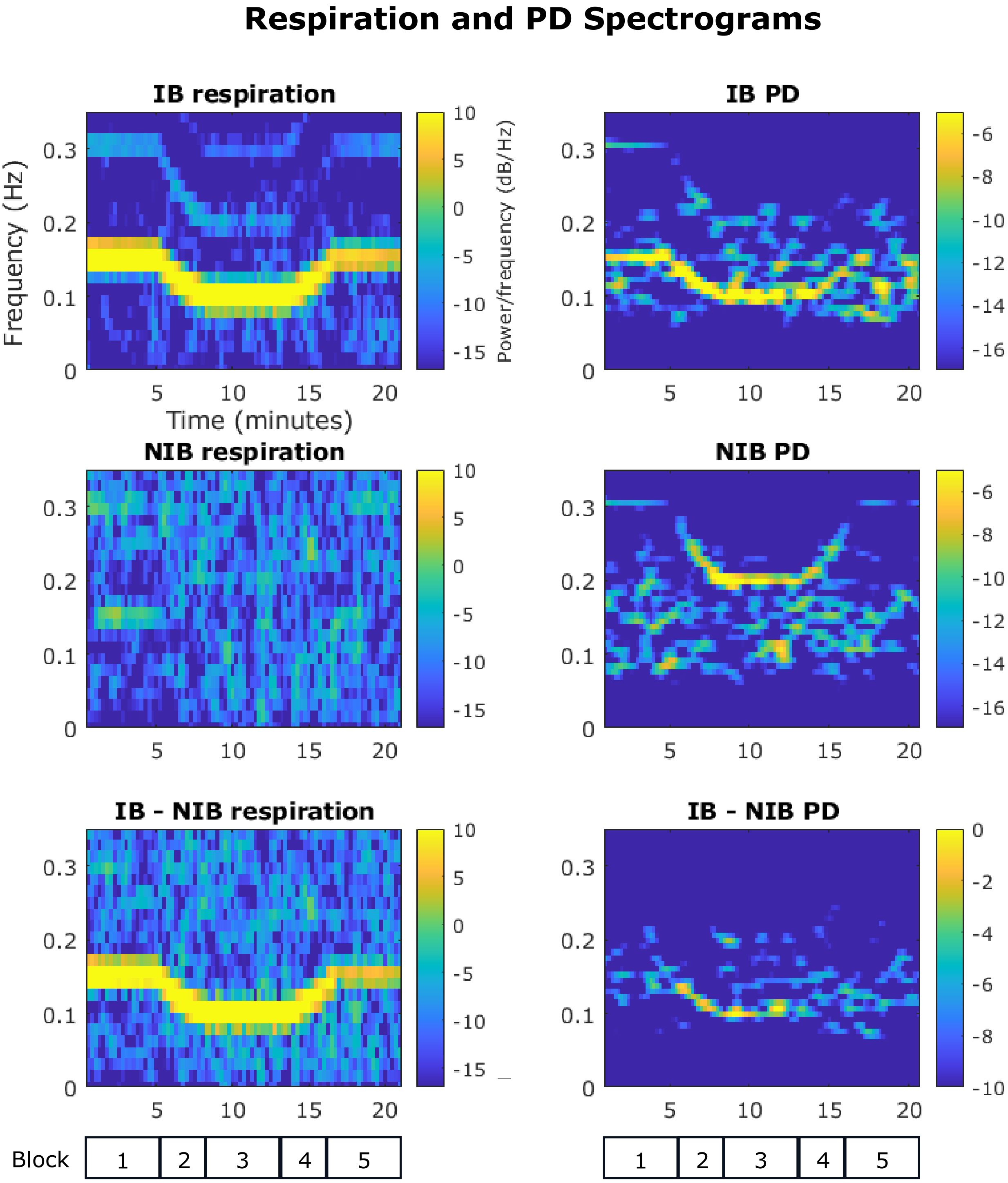


Figure 1.5 - Spectrograms across the whole task for respiration (left) and PD (right). PD signals were high pass filtered at 0.075 Hz for display purposes.

(1)(iii) Does SPB affect the phase coupling relationship between respiration and PD?

Phase Locking Analysis

Since the guided respiratory frequencies overlap significantly with PD frequencies, we sought to characterise this coupling relationship with phase locking analysis.

At the whole task level, phase locking values (PLVs) obtained were: IB group ranged 0.002 - 0.35, M = 0.16 ± 0.016, NIB 0.005 - 0.21, M = 0.06 ± 0.01. The IB group mean was significantly higher, t(41) = 4.81, $p < 0.001$. IB group mean phase offset between respiration and PD was -0.36 rad ± 0.15 and NIB was -1.36 rad ± 0.12 (interpret as PD negatively shifted in phase with respect to respiration for both) (Figure 1.6). These mean phase offsets were significantly different, F(41) = 20.97, $p < 0.001$, the IB phase angles being closer to 0 rad.

Investigating an effect of blocks on PLVs, RM-ANOVA across blocks 1, 3 and 5 showed no significant main effect of blocks, F(2) = 0.33, p = 0.72, a significant main effect of group, F(1) = 39.08, $p < 0.001$, with higher PLVs in the IB group in all blocks, and no interaction, F(2) = 1.61, p = 0.21.

The mean phase offset appeared to shift over the blocks (Figure 1.6), however a Harrison Kanji test only showed a significant main effect of group $\chi2(1) = 31.68$, $p < 0.01$, and no effect of block, $\chi2(2) = 4.09$, $p = 0.13$, nor interaction, $\chi2(2) = 4.62$, $p = 0.95$.

A grand moving average plot of PLVs across the whole task (Figure 1.7) shows that the PLVs for the IB group remain higher than the NIB group until the very end. Further, there is an indication in the IB group of PLV increasing through blocks 1 and 2, plateauing at the maximum across block 3 and then decreasing back during blocks 4 and 5. A running t-test across time shows most significant differences between the groups at $p < 0.001$ lie toward the end of block 2 and throughout 3. PLV in the NIB group stays fairly consistently low, however there is a sharp rise at the end of block 5 which makes it comparable to IB.

To determine whether task PLVs obtained were significantly above chance (1.65 std), actual PLVs were compared to surrogate PLVs. 18/23 IB group participants had PLVs that were significantly greater than surrogate, with a group mean of 3.43 std ± 0.44 above the surrogate mean. 15/20 NIB group participants' PLVs were significantly greater than the surrogate, M = 2.77 std ± 0.46. The group difference in 'stds above the surrogate' was not significant, $t(41) = 1.03$, $p = 0.31$.

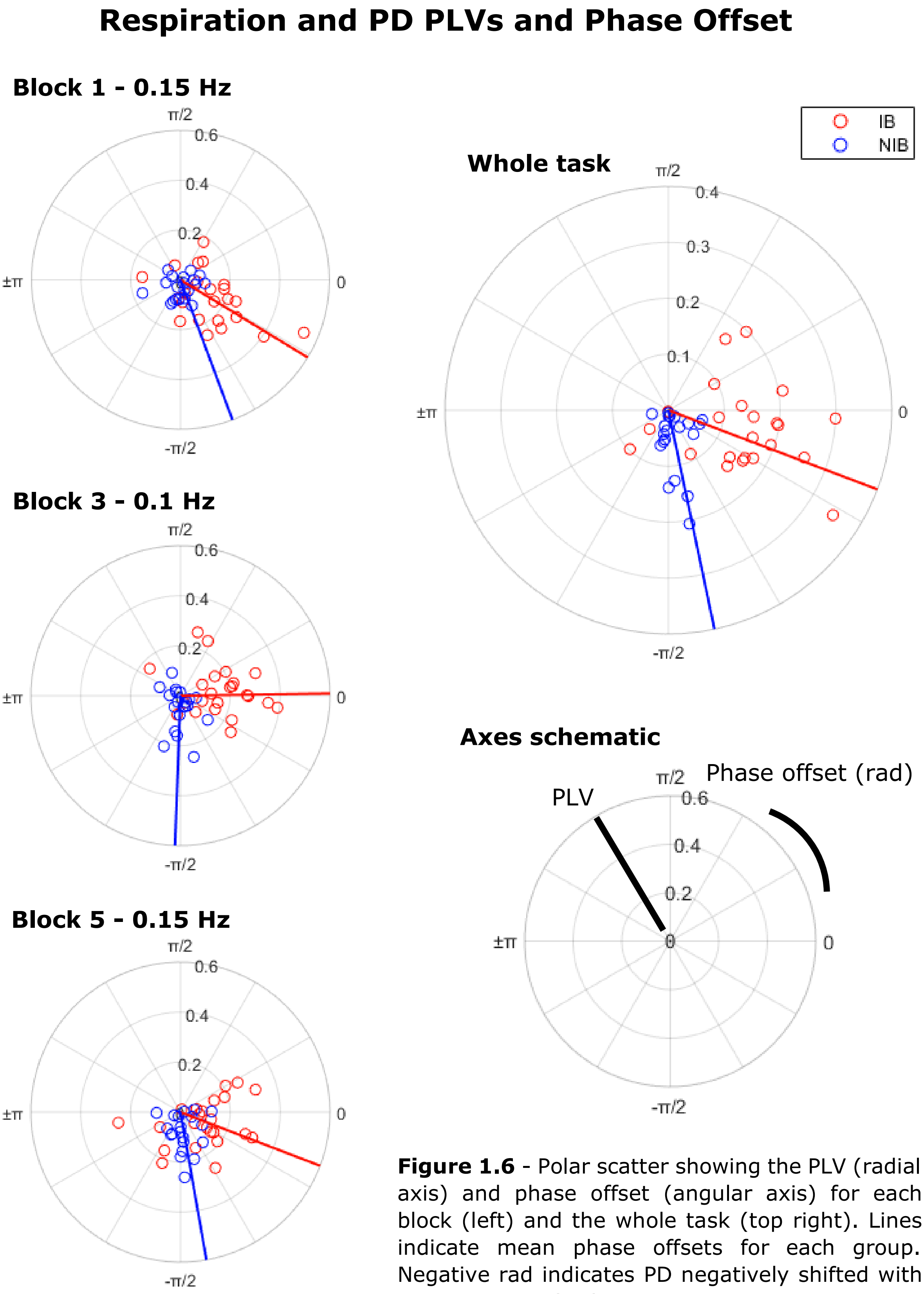


Figure 1.6 - Polar scatter showing the PLV (radial axis) and phase offset (angular axis) for each block (left) and the whole task (top right). Lines indicate mean phase offsets for each group. Negative rad indicates PD negatively shifted with respect to respiration.

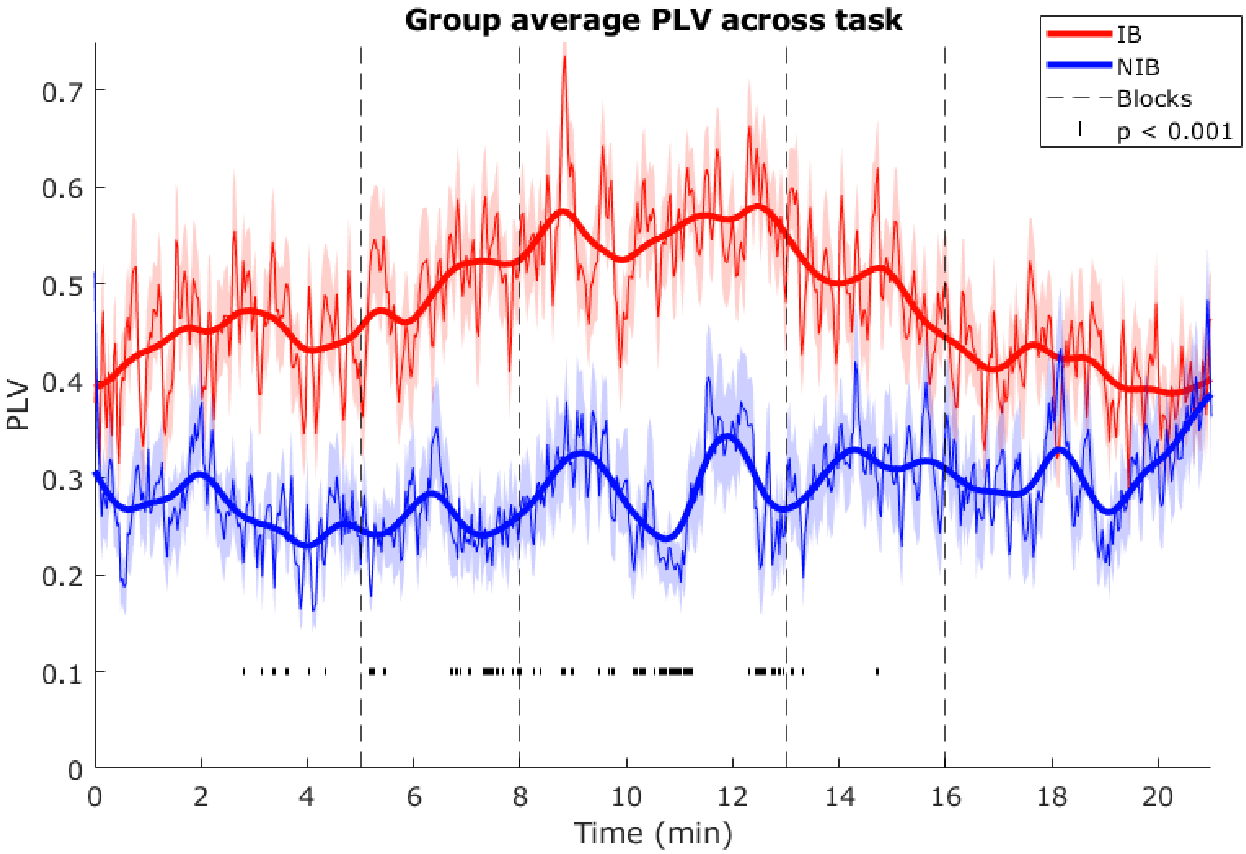


Figure 1.7 - PLV moving average across the task. Thicker lines represent a smoothed mean for each group. Dotted vertical lines indicate blocks and small dashes along the bottom indicate where groups differ at $p < 0.001$.

PD Over the Respiratory Cycle

To characterise the respiratory-PD coupling on a breath-by-breath basis, we plotted changes in PD over the respiratory cycle for each of the three blocks (Figure 1.8). In the IB group, PD shows an initial sharp rise with inhalation onset, a slight plateau, a gradual second rise from late inhalation to early exhalation, and then a steady decrease. In block 3, the NIB group plot line deviates from 0, indicating some PD modulation, and in block 5, PD follows a stronger pattern, being lower during inhalation and higher in exhalation. Importantly, the PD modulation patterns are phase shifted relative to the respiratory cycle, and thus, ruling out the possibility that changes in PD are simply due to movement artifacts over the respiratory cycle.

(2) Do respiratory-related PD oscillations correlate to any behavioural outcomes?

Since we discovered PD oscillations overlapping with respiratory frequencies, we tested for significant relationships between the power of these PD oscillations and our attentional behavioural measures. We also tested this with the additional peaks at 0.2 Hz and 0.3 Hz.

Circular-linear correlations between RTm phase and PD peak power at 0.1, 0.15 Hz for IB, and 0.2, and 0.3 Hz for both groups, showed no significant results. Pearson’s correlation for RTVL and PD power at 0.3 Hz, both groups combined, was significant, r(41) = 0.37, p = 0.015. However, Bonferroni correcting for multiple comparisons at p < 0.013 makes this a near-threshold non-significance.

In the NIB group both IR (r(18) = -0.48, p = 0.03) and Switches (r(18) = -0.6, p = 0.005) significantly correlated with PD power at 0.3 Hz which survived multiple comparison correction. Switches and PD 0.2 Hz power showed a trend, r(18) = -0.42, p = 0.067.

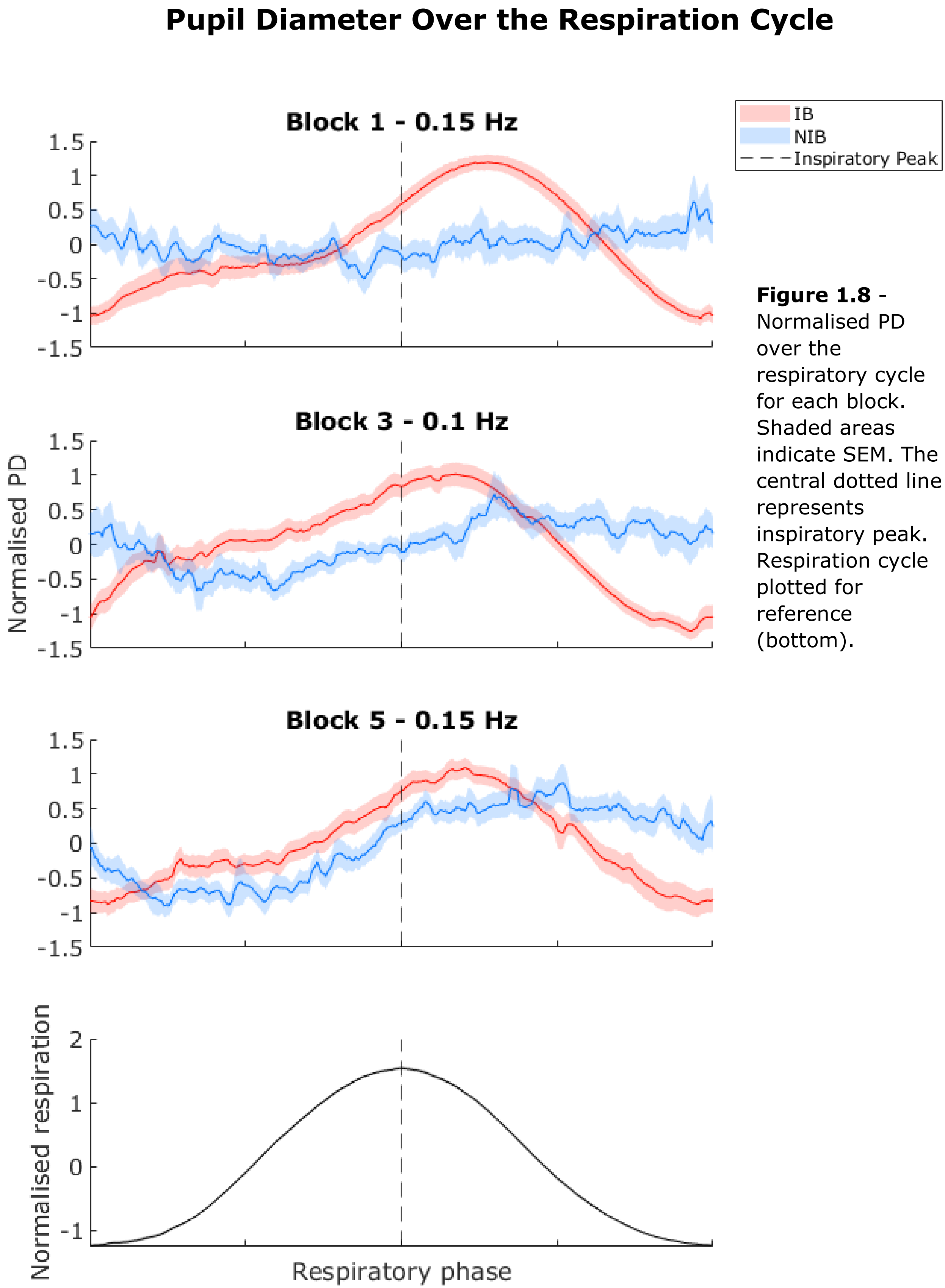


Figure 1.8 - Normalised PD over the respiratory cycle for each block. Shaded areas indicate SEM. The central dotted line represents inspiratory peak. Respiration cycle plotted for reference (bottom).

Discussion

The relationship between attention and breath is of central importance in traditional forms of meditation practice, but how respiration and attention influence each other from a psychophysiological perspective is underexplored and requires a novel paradigmatic approach. The present investigation sought to assess a link between slow paced breathing (SPB) and stable attention. Using pupil-linked arousal as an LC proxy measure, we sought to provide evidence for a dynamical systems model (Melnychuk et al., 2018, 2021), which posits that respiration, LC-noradrenaline, and attention are autonomous oscillators that either tend towards stable attractor inter-dynamics, regularising the attentional oscillations that accompany the breath, or evolve toward a decoupled state increasing variability and instability of attention. We hypothesised that a manipulation of SPB would push the system toward increased attentional stability concomitant with a reduction in PD oscillation frequency.

We found evidence for both. Despite not showing behavioural group-differences in our predefined RT measures, SPB was highly related to maintaining the correct response rhythm over time. Additionally, PD oscillations were closely entrained to the slow rhythm of the breath in this group. We characterised this link further, observing a greater phase-phase coupling strength, smaller phase offset, and a greater phase-amplitude modulation of PD compared to controls.

To test our hypotheses, we constructed a novel task, the PACE task, to serve as a simultaneous breath guide and attention monitoring task. To our knowledge this is the second study to implement a breath guide during a task (see D’Agostini et al., 2022), and we demonstrated the feasibility of doing so.

Attentional Stability

With regards to our predefined behavioural metrics of attentional stability, we found no evidence that the presence or rate of our guided breath intervention impacted response time accuracy (RTm) or variability (RTVL) in our task. This was unexpected as we thought that either the breath task would complement performance in the clicking task, in line with the coupling model, our favoured hypothesis, or alternatively, that there would be a ‘dual task interference effect’ in the IB group, where performance would decline in both the ‘breath task’ and ‘clicking task’. The comparable performance within and between groups for RTm and between groups for RTVL indicates that there is perhaps a ceiling effect in the PACE task, i.e., its demands are not sufficiently difficult or complex enough for variability in performance to arise between individuals or experimental conditions. Future iterations of the PACE task could include a more sensitive measure of attentional stability to rule out this possibility.

However, an exploratory analysis of incorrect response rhythms, IRs and Switches, provided some behavioural discrimination between the groups. IB participants gave very few IRs, whereas NIB had a mean of 58 counts, with a lot of inter-participant variability. The NIB group's IRs appeared to be less likely during blocks 2 and 4 where the tone cycle rate was changing, perhaps this dynamic element engaged their attention more. The significant negative correlations within the IB group for respiratory-tone entrainment and IRs and Switches provide further evidence that adhering to the breath guide aided attentional stability. There were intriguing significant correlations within IB between IRs and Switches, with the Mood Repair facet of the Trait Meta-Mood Scale. One tentative interpretation could be that the meta-cognitive abilities that aid Mood Repair, translate to "Attention-Repair" also. Taking these two aforementioned IB correlations together, IRs and Switches were infrequent in this group however when they did occur it was likely due to poor adherence to the breath guide, or a lesser trait ability of reorientating mood.

The positive findings for IRs and Switches but not for RTm and RTVL imply that the groups differed in their longer-term attentional state fluctuations, rather than shorter term trial to trial variability. This is fairly consistent with a study that has shown a positive influence of SBP on 'error monitoring' (Hoffmann et al., 2019), and so, perhaps the effects of SBP are more related to mitigating lapses in attention. In addition, NIB responses to the qualitative questionnaire were more negative than IB responses with respect to following the tasks demands.

The IB group essentially had two cues to support maintaining the correct response rhythm over time, the auditory rhythm and their respiratory rhythm. Should attention fail to recognise the auditory tones momentarily, the interoceptive cue of the breath may have acted as a backup. The question then arises as to whether this particular 'attentional anchoring' is a breath-specific phenomenon. Up to a point, increasing the demand of a task should encourage engagement, especially demands geared towards the same rhythm. From the present experiment, it cannot be ruled out that if the NIB group had an additional, internal, temporal cue, such as numerical counting, they could show comparable response rhythm errors to the IB group. Future iterations using the PACE task should seek to control this group difference. Having said this, in the following discussion of our respiration-PD findings we offer a possible explanation as to how the breath may modulate attention via the LC-NA system.

Respiratory-PD Coupling

Through multiple analyses we show that SPB had a remarkably strong effect on modulating PD oscillatory frequency, bringing it into the same rate as respiration. The phase offset between respiration and PD also differed between groups, being closer to 0 in the IB group, especially during the slowest breathing. So, not only were the signals oscillating at a similar rate, but they were also more in-phase.

Despite an insignificant block-wise comparison of PLV, the moving window PLV provided an insight into the trend over time (Figure 1.7). PLV appeared to be higher for IB vs NIB across the whole task until the very end, being highest during blocks 2 (slowing: 0.15 → 0.1 Hz) and 3 (slowest: 0.1 Hz). This is further corroborated by the group difference in PD power at respiratory frequency in these blocks (Figure 1.5). It possible that slower respiration facilitates stronger coupling, however there are a number of other considerations. Although there is clear 0.15 Hz PD power in IB during block 1, there appears to be some here for NIB also. Possibly as NIB show their highest auditory-respiratory entrainment during block 1, evidenced by vector lengths (Appendix 1; Figure S1.2b) and respiratory spectrogram activity (Figure 1.5). However, neither the moving window PLV (Figure 1.9) or the 'PD over respiratory cycle' plot (Figure 1.8) indicate particularly strong coupling. On the contrary, this *is* evident in these plots for NIB in block 5 (0.15 Hz), with PLV rising sharply towards the end of the task, and PD appearing to be slightly modulated over the respiratory cycle. Additionally, IB respiratory-entrainment and 0.1 Hz PD activity drops off in block 5, possibly explaining the lesser group difference here. This sharp rise for NIB towards the end is intriguing; it's possible that without any breath manipulation, respiratory-PD coupling naturally arises after this amount of time, at least under these relatively low cognitive demands. It does appear as though NIB PD is more modulated over the respiratory cycle in block 3 vs 1, and again in 5 vs 3 (Figure 1.8). One further consideration for the lesser block 1 difference, and a general limitation of the study, is the issue of harmonic frequencies. We discovered additional PD oscillations at 0.2 and 0.3 Hz in both groups. It's possible that in our frequency-power analyses, activity in this range is additionally represented by the harmonic frequencies, e.g., 0.3 Hz PD activity could also show up as 0.15 Hz activity. Since the power of these did not differ between groups, we interpret them to be stimulus and/or response driven oscillations. The PD power at 0.3 Hz showed some relationship with RTVL and IRs which does implicate it as a performance-sensitive signature.

Our findings are at odds with the conclusion from a recent review on the topic of 'respiratory modulation of PD', which concluded that evidence for an effect of respiration rate was "very low" (Schaefer et al., 2023). They included eight studies which directly tested this, and the results were mixed. Four studies showed an effect (Calcagnini et al., 2000; Daum & Fry, 1981; Murata & Iwase, 2000; Yoshida et al., 1994) and the other four, with the larger sample size (n > 15), were reported to have shown no effect (Bouma & Baghuis, 1971; Schumann et al., 2015, 2017, 2020), although it appears to us that Schumann et al., (2020) did show modulation through a slow breathing test (6 breaths per minute). Confusion likely arose due to the authors using "deep" and "slow" interchangeably – the review recognised an effect of depth. All but one of these studies primarily correlated pupil activity and respiration at rest without any respiration intervention (except Schumann et al., 2020 also). This study from Daum & Fry (1981) was similar to the present study, using auditory stimuli to guide the breath in the range 0.1 – 1 Hz and measuring pupil components. In contrast, they only included 3 participants, trials were 30 s long, and the pupil activity was broken down into discrete frequency components by their convolution method. Despite the differences, their plot of the slow component of PD during 0.1 Hz respiration was remarkably similar to our own: an initial rise with inhalation onset, a slight plateau before a second steady increase, and dropping in early-mid exhalation. However, their plot for the 0.15 Hz respiration was not similar, appearing 180 deg out of phase. Overall, their findings support a respiratory rate modulation of PD over a wide range of respiratory frequencies.

This review additionally did not include a study from Parnandi & Gutierrez-Osuna (2013) who investigated estimating heart rate variability from PD. They had their 5 participants breathe at 6 (0.1 Hz), 9 (0.15 Hz) and 12 (0.2 Hz) breaths per minute which resulted in clear PD spectral peaks at the respiratory frequencies. This also supports the present study's findings.

Respiration-LC-Attention Coupling

Beyond evidencing a respiratory-pupillary coupling relationship, the present study sought to link this with attentional stability, in line with the respiration-LC-attention coupling model from Melnychuk et al., (2018). We investigated this from the perspective that PD is an established proxy measure for LC-NA activity (Bang et al., 2023; DiNuzzo et al., 2019; Elman et al., 2017; Meissner et al., 2023; P. R. Murphy et al., 2014). The specific hypothesis tested was that reducing respiratory frequency reduces LC-NA tonic (pupillary) oscillations, which stabilises attention. We found evidence to support both aspects separately, but it is not possible from our findings to conclude a causal link between them. Since the groups differed only in IRs and Switches, a significant correlation between these and a measure of respiratory-pupillary coupling would have supported a causal link, however this was not found. The IB group had low counts of these lapses and the NIB group had low respiratory-pupillary coupling, and so these data may be insufficiently powered to test for such a correlation. Having said this, we do report significant correlations between these lapses and respiratory entrainment, and lapses and Mood Repair for IB.

In the following, we entertain the possibility of a causal link between SPB and attentional stability via the LC through the perspective of the respiration-LC-attention coupling model (Melnychuk et al. 2018) and provide possible explanations of our findings:

The LC-NA system is often discussed in relation to a proposed role as a facilitator of attentional flexibility. An influential model, the Adaptive Gain Theory (Aston-Jones & Cohen, 2005b), describes how the LC receives resultant information from evaluating the perceived reward/utility of exploiting a current focus, and either facilitates currently engaged networks through task-locked phasic burst firing, or, encourages exploration for an alternative focus through task-indiscriminate tonic firing. A balanced strategy employing both phasic and tonic 'modes' likely underlies the experience of attentional state fluctuations and should aid the achievement of long-term goals. However, what if the long-term goal is attentional *stability*, as it is here in the present study?

Previous studies investigating pupillometry signatures related to sustained attention have typically used sudden onset stimuli and noted the pre-stimulus baseline (tonic) and stimulus evoked (phasic) components of PD (Benitez & Robison, 2022; Martin et al., 2022; Unsworth et al., 2022; Unsworth & Robison, 2016, 2018). From this perspective, successively sustained attention would be reflected in consistent PD signatures over time i.e., constant tonic level and phasic amplitudes, indicating a maintenance of the task-focused "phasic mode" of the LC.

Instead, what we believe we show here is a cyclic fluctuation in tonic PD, entrained by the stimulus in both groups, but crucially, additionally entrained by respiration in IB, resulting in a higher attentional stability in this group. In the NIB group, attentional stability would have been largely due to top-down control to the auditory stimuli, reflected in auditory-PD entrainment, and subject to ongoing motivational/utility evaluations. According to Adaptive Gain Theory (Aston-Jones & Cohen, 2005b), a drop in perceived utility would have been reflected in high tonic PD, led to a focal reorientation, and then depending on the time of task re-engagement, participants may have returned with an incorrect response rhythm. In contrast, the IB group additionally had the bottom-up influence of respiration on PD tonic levels. It should also be noted that since our participants were breathwork naive, there would have been a considerable top-down attentional component on maintaining the respiratory rhythm. These additional influences on PD/LC-NA may somewhat override endogenously driven attentional reorientations. Additionally, it is possible that this top-down attention on the guided respiratory rhythm could have been a driver of the observed PD oscillations. Considering that the rhythm of the stimuli induced PD entrainment in the NIB group, its possible that the IB group were similarly sampling the rhythm but at half the rate due to its implications for their breath. Future studies using individuals experienced with breath work and having participants guide their own slow breathing may provide clarity here.

Regardless, such periodic fluctuations in tonic LC firing would induce a high degree of predictability into the system, reducing the chance of unexpected attentional orientations and therefore increasing attentional stability. Respiration has indeed recently been conceptualised as a signal that enhances predictability through multiple pathways, including the LC-NA system (Brændholt et al., 2023), and higher-order pathways to the insular cortex, which processes interoceptive signal information (Allen et al, 2022).

Respiratory information could reach the LC through a number of possible pathways: The preBötzinger Complex (preBötC), a medullary neural network and respiratory pattern generator (Muñoz-Ortiz et al., 2019), projects to the LC in mice (Yackle et al., 2017). Ablation of this subset of neurones by Yackle et al., (2017) mediated arousal only, inducing a prevailing calm state whilst leaving their regular breath pattern intact. The preBötC burst fires in time with inspiration (Morgado-Valle et al., 2015), and if these excitatory LC projections exist in humans, SPB may periodically innervate the LC, stabilising arousal and attentional states. A considerable number of LC neurons are CO_2 sensitive in mice and rats, responding in a dose dependent manner to hypercapnia (Gargaglioni et al., 2010) and relaying this information to other key respiratory areas (Krohn et al., 2023; Lopes et al., 2016). This raises the possibility that periodic fluctuations in CO_2 over respiratory cycles could be registered by the LC in humans. Vagal afferents from pulmonary stretch receptors relay respiratory information to the nucleus tractus solitarius (Kubin et al., 2006; Schelegle, 2003) which has itself been suggested to project this to the LC (Melnychuk et al., 2018; Noble & Hochman, 2019). During normal breathing, pulmonary vagal afferents are innervated via rapidly adapting receptors which produce phasic bursts in time with early inhale, and during deep breathing, slowly adapting receptors are additionally activated throughout the duration of late inhalation. Our IB participants did indeed breathe deeper than NIB (in blocks 1-4, block 5 is similar; not reported here) and so they were likely recruiting both inspiratory-associated receptors. This raises the possibility of cyclic vagal information reaching the LC. A two-step increase would align with our PD pattern over the respiratory cycle (Figure 1.8), however, precise connections to the LC are unclear here and they have been proposed to be inhibitory (Noble & Hochman, 2019), which would not explain our pattern of increase.

These aforementioned candidate pathways still remain speculative and primarily based on animal and in vitro models. However, our present findings in conjunction with Melnychuk et al.'s findings of respiratory-PD (2018; 2021) and respiratory-LC fMRI BOLD (2018) synchronisation provide evidence of a linkage nonetheless.

Strengths and Limitations of the Paradigm

As a breath guide, IB participants generally entrained well by attuning their breath to the appropriate rate. However, entrainment did decrease steadily across the task. Other 'time on task' decrements in engagement were evident, with block 5 showing the lowest RTVL and the highest counts of IRs and Switches for both groups (Figure 1.3). Considering that we implemented guided breathwork to a group who were naive to such a practice, they maintained the rhythm well. It is worth noting that participants’ resting respiration rate did not correlate with the degree of entrainment in the task.

IB participants entrained their breath stronger to LH than HL tone transitions (Figure S1.2b). One interpretation would be that it is more difficult to detect the precise onset of the lower frequency tone than the higher. However, this is at odds with the finding that RTVL is higher for HL than LH (Figure 1.3a), indicating a lower variability in detection time. Importantly, this latter finding is present in both groups, implying that it is stimulus specific. Thus, it appears as though LH lent itself to respiratory entrainment and HL lent itself to response entrainment. Respiratory-LH entrainment meant aligning inhalation onset with the beginning of the tone, which would be consistent with the inhalation bias of the majority of recent findings regarding respiration-task event entrainment (Kluger et al., 2021; Perl et al., 2019; Zelano et al., 2016). Although the LH/HL RTVL difference is consistent across groups, stimulus properties should ideally be altered to minimise this effect in future iterations of the PACE task.

Although IB attuned their respiration *rate* according to the task instructions, there was a consistent phase difference between respiration phase onset and tone transition whereby they began inhaling/exhaling prior to the tone transition time (Figure S1.2c). Additionally, the breath onset was significantly earlier in block 3 (0.1 Hz). This is not of major concern with regards to our study manipulation, changing respiratory rate, however it would be if one is studying phase-specific task events. It would be interesting to observe whether this anticipatory phenomenon occurs in individuals familiar with guided breathwork.

NIB participants did show some evidence of auditory-respiratory entrainment, despite no explicit instructions to do so. Half the participants in this group had significant non-uniformity with regards to entraining their breath to the tone transitions and the auditory-respiratory vector lengths ranged low-medium. Additionally, on the NIB respiratory spectrogram there is an indication of consistent 0.15 Hz activity during block 1. Our chosen stimuli were based on existing breath guides and were meant to be intuitive for the IB participants to follow, especially since they were breathwork naive. Those NIB participants who explicitly mentioned entrainment in the qualitative questionnaire were excluded from analyses and otherwise we deemed the group’s entrainment to be mild enough to consider them as a control group. This of course, however, does not rule out the possibility of any effect from this level of entrainment. NIB auditory-respiratory entrainment appeared to encompass late exhalation to early inhalation. Interpretations from this are limited due to the mildness of entrainment, however it is worth noting that a previous study have found an exhale preference for response entrainment (Johannknecht & Kayser, 2022). The mean entrainment angle for LH was significantly later in the breath cycle than HL, encroaching into early inhale. An area for future investigation may be how stimulus features affect respiratory entrainment behaviour.

As an attention task, the PACE task appeared comprehensible to most participants judging from the subjective reports. However, there was the unintended but frequent issue of participants losing the correct left/right response rhythm with no prompt to aid a return to this. Fortunately, this ended up becoming a useful variable in discriminating the groups (IRs, Switches). Response rate was actually higher than 100% for most participants, implying that false alarms are more likely than omissions in this task. However, this only amounted to both groups averaging an extra 5% response rate (17 clicks).

Concluding Remarks

Here we have demonstrated with a novel task that slow paced breathing was not associated with trial-to-trial response time accuracy, but with a reduction in response key errors derived from an exploratory analysis. We provided a possible mechanistic explanation for this by showing significant respiratory modulation of pupil diameter, implicating the locus coeruleus arousal and attentional system. These findings contribute to a scarce literature on a topic which has been central to meditative practices for millennia and contributes to the emerging recognition of the role of respiration in cognitive neuroscience.

Appendix 1 – Manipulation checks and task validity

Is the PACE task effective as a paced breath guide and sustained attention test?

To justify the analyses investigating an effect of slow-paced breathing (SPB) on attention and pupil diameter (PD), we first had to establish whether the novel PACE task was effective as a sustained attention test and paced breath guide. Six NIB and one IB participant(s) were excluded due to incomplete data collection (n = 59; NIB n = 32, IB n = 27).

PACE Task - Sustained Attention Task – Both Groups

Non-compliance to responding was evident in 2 IB participants, clicking 0% and 70% of the expected 340. They were both excluded from subsequent analyses (IB n = 25). Otherwise, participants responded >99% of expected clicks and actually tended to exceed 340, seen by the mean proportion of 'clicks out of expected': IB M = 1.05 ± 0.01, NIB M = 1.045 ± 0.01. Figure S1.1 shows this metric across the blocks. Testing for differences here showed that there was no significant effect of blocks, F(4) = 0.91, p = 0.46, nor group, F(1) = 0.98, p = 0.33, nor interaction, F(4) = 0.43, p = 0.79.

To assess the tasks accessibility subjectively, we asked participants '*Were you able to easily follow along with the tones using mouse clicks?*'. 44/57 participants (20 IB, 24 NIB) gave a solely positive response with regards to this. 7 participants (3 IB, 4 NIB) gave mixed responses, citing difficulty in tone discrimination or mixing up the left/right clicks. 6 participants (1 IB, 5 NIB) gave a majorly negative response, 3 zoning out from the beginning, 2 forgetting the left/right click order completely, 1 couldn't tell the tones apart and 1 giving no reason.

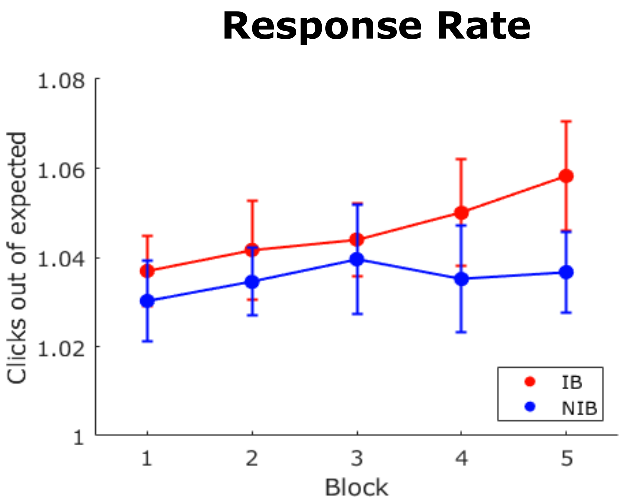


Figure S1.1 -

Proportion of clicks made out of the total expected across blocks. Error bars represent the standard error of the mean.

PACE Task - Auditory-Respiratory Entrainment – IB Group

To assess whether the PACE task as effective as a paced breath guide for the IB group (n = 25), we analysed the respiratory phases at tone transition time to see if they were aligned and consistent. Rayleigh tests rejected the null hypothesis of uniformity for of respiratory phases at both LH and HL transitions for all IB participants, all p values < 0.001, indicating significant clustering. Resultant auditory-respiratory vector lengths ranged between 0.34 - 0.97 for LH; M = 0.86 ± 0.03 and 0.23 - 0.97 for HL; M = 0.81 ± 0.04 (Figure S1.2a). Two IB participants appeared to entrain relatively poorly, exhibiting low LH and HL vector lengths that were comparable to the NIB group. They were therefore excluded from subsequent analyses as they could not be considered to have followed the paced breathing intervention sufficiently (IB n = 23). Without these participants, all IB auditory-respiratory vector lengths were > 0.58.

Examining the mean respiratory phase angles that the auditory-respiratory vector lengths tended towards, the IB group level pattern for entrainment shows that they already began inhaling or exhaling prior to tone transition points, as indicated by mean phase angles at these times: LH = -2.52 rad, HL = 0.91 rad, representing early inhale and early exhale respectively (Figure S1.2c). These angles differed across blocks 1, 3 and 5 as seen by Watson-Williams test: HL $p < 0.001$, LH $p = 0.003$, with block 3 (HL = 1.2 rad, LH = -2.3) showing the mean respiratory angle further into the inhale and exhale than in blocks 1 (HL = 0.84, LH = -2.6) and 5 (HL = 074, LH = -2.6).

Entrainment appeared to diminish over the course of the task, represented by a significant difference in auditory-respiratory vector lengths across blocks, decreasing for both LH, $F(4) = 5.43$, $p < 0.001$, and HL, $F(4) = 9.58$, $p < 0.001$.

IB group participants appeared to entrain more tightly with LH than HL transitions, with the task level mean LH vector length being significantly larger, t(22) = 3.93, $p < 0.001$. Differences appear to emerge later on in the task (Figure S1.2b).

See Figure 1.5 for the group average spectrogram of respiration over the task to note how the respiratory frequency changed over the task. It is additionally worth noting that participants' resting respiration rate did not correlate significantly with any entrainment metric and thus the ability to follow the guided breath rates was likely independent of this.

Auditory-Respiratory Entrainment - NIB

We also checked for evidence of respiratory entrainment in the NIB group to see if this occurred without any explicit instruction to (n = 32).

For a subjective assessment, we asked participants '*How much attention did you pay to your breath during the study?*'. 7 NIB participants made reference to some degree of focus on the breath, 4 explicitly mentioning aligning the tones with the breath. 3 of those 4 participants were previously excluded for incomplete data and the remaining 1 was excluded from subsequent analyses based on this comment and relatively high auditory-respiratory vector lengths (M = 0.41). The other 3/7 mentioned some other aspect of breath e.g., depth. Besides these notable exceptions, it appeared as though the NIB group was generally naive to the guided breath aspect. When asked: *'What did you think the point of this study was?'* 8 NIB participants mentioned 'breath', but it was often in conjunction with 'heart rate' or 'eye movements', and no participant made any explicit reference to guided breathing.

Rayleigh tests showed 5/32 NIB participants with significant non-uniformity ($p < 0.05$) for LH only, 3/32 for HL only and 16/32 for both. Therefore, 24/32 NIB participants showed some significant degree of respiratory entrainment to the stimuli according to this metric. Auditory-respiratory vector lengths for the NIB group were: LH ranged 0.04 - 0.39, M = 0.17 ± 0.015; HL, 0.03 - 0.43, M = 0.17 ± 0.02. Nearly all of the mean phase angles for each NIB participant at the time of tone transitions lay between early-mid exhale to early inhale (Figure S1.2c). The mean phase angle for LH was slightly later in the exhale, 2.79 rad, than for HL, 2.08 rad, with a Watson-Williams test indicating a significant difference, $F(1) = 6.81$, $p = 0.01$.

There was a significant difference across blocks for HL vector lengths, $F(4) = 3.96$, $p = 0.005$ (Figure S1.2b), with post-hoc Holm tests showing significant decreases between blocks 1 and 3 and blocks 1 and 4 (both $p < 0.01$). There was no significant difference across blocks for LH vector lengths, $F(4) = 1.60$, $p = 0.20$. There was no significant difference between LH and HL vector lengths at the task level.

It is worth noting here that the spectrogram for NIB respiration (Figure 1.5) shows some activity at 0.1 Hz during block 1, and then the rest appears more random.

Despite showing evidence of respiratory entrainment to tones, i.e., significant Rayleigh test non-uniformity and small-medium respiratory vector lengths, the NIB group did this to a considerably lesser extent and with a different phase pattern when compared to the IB group. We believe that the entrainment was subtle enough to continue with the further analyses comparing the groups for an effect of instructed SPB.

Entrainment Measures

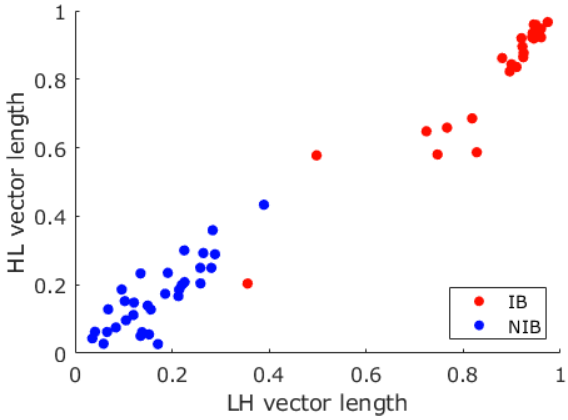


Figure S1.2a - Task level mean auditory-respiratory vector lengths, representing the degree of respiratory entrainment to tone transition times, HL and LH.

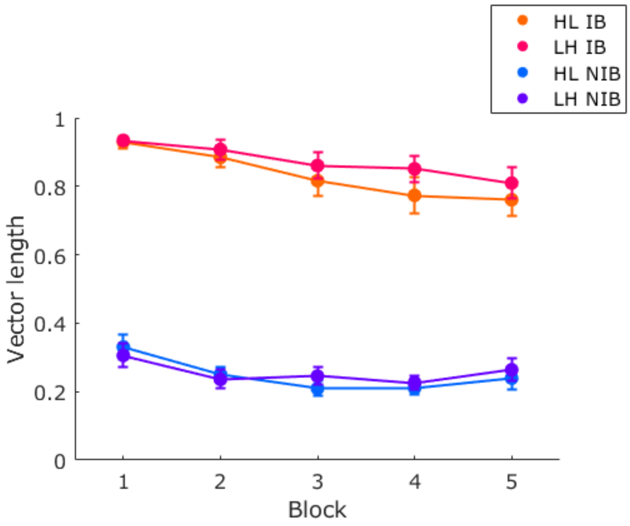


Figure S1.2b - Mean auditory-respiratory vector lengths at each block, split by tone transition type and group. Error bars represent the standard error of the mean.

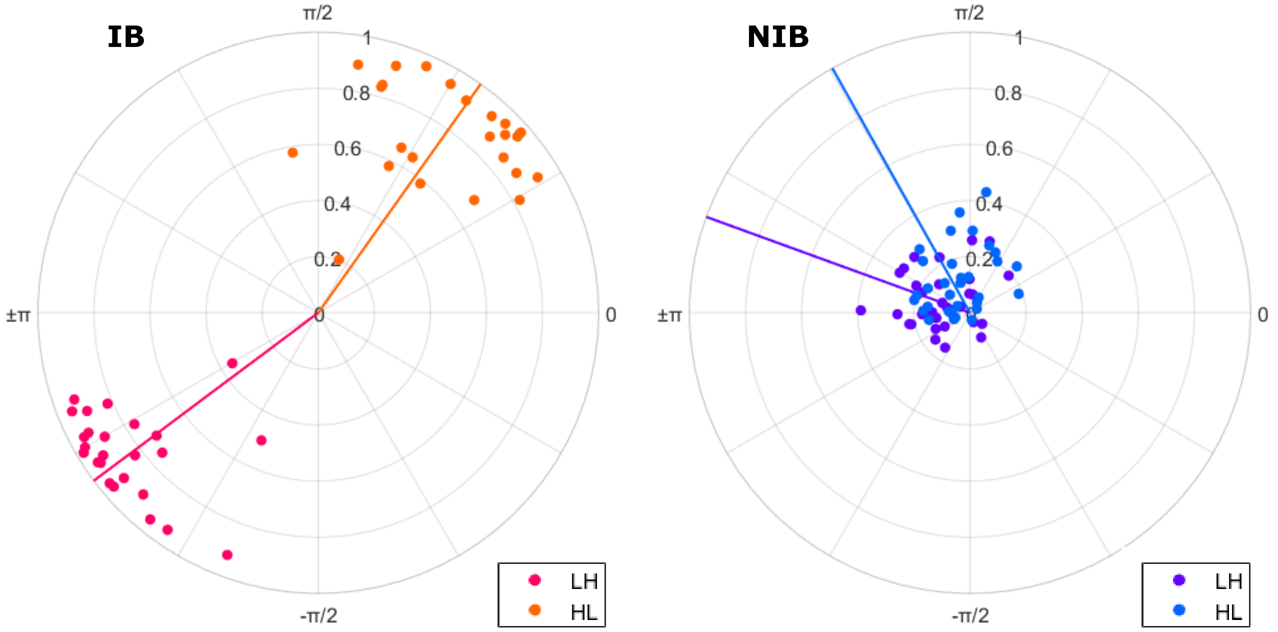


Figure S1.2c - Task level mean auditory-respiratory vector lengths (radial axis) and the mean phase angle of entrainment (angular axis) split by tone transition type. Lines indicate the mean phase angle for each group. Phase 0 rad is exhale onset and the breath follows anticlockwise.

Empirical Chapter 2

Introduction

Long been the domain of yogis and other meditators, neuroscience is increasingly recognising that respiration adapts to and influences our cognitive experience in an ongoing and fundamental manner (Allen et al., 2023; Engelen et al., 2023; Varga & Heck, 2017).

An increasingly observed phenomenon in evidence of an interplay between respiratory and cognitive dynamics is that respiration entrains to task events such that certain respiratory phases (i.e., inhale, exhale) occur preferentially at the times of task stimuli presentations and responses. This has been observed across a range of sensory-cognitive domains such as: visual lexical memory (Huijbers et al., 2014), auditory oddball (Melnychuk et al., 2018), visuospatial (Perl et al., 2019), tactile perception (Grund et al., 2022), auditory perception, emotional discrimination, visual motion and visual memory (Johannknecht & Kayser, 2022). In addition, respiration entrains to voluntary motor actions (Park et al., 2020). These wide-ranging entrainment effects highlight the breadth of adaptability of respiration under different sensory-cognitive demands.

Moreover, respiration is not only adapting, but entrainment in those studies was often concurrent with a modulation of task performance and/or perception, i.e., participants were better or worse at a task or perceiving near threshold stimuli depending on their current respiration phase. Respiration phase may therefore at least partially account for cognitive-behavioural variability in a way not previously considered. Further examples of respiratory modulation of cognition/perception have been seen for visual memory retrieval (Nakamura et al., 2018), visual perception (Flexman et al., 1974; Kluger et al., 2021), awareness of visual perception (Leupin & Britz, 2023), pain perception (Arsenault et al., 2013; Iwabe et al., 2014), and perception of quantities (Belli et al., 2021). It is important to note that these entrainment and cognitive-modulatory effects have been observed without any respiratory manipulation and presumably unknowingly to the study participants. The unconscious perception of internal states and the influence this has on cognition has been referred to as ‘implicit interoception’ (Murphy et al., 2016). This has mainly been studied with regards to cardiac influences, however an additional and perhaps complementary role of respiration is becoming increasingly apparent from these recent findings.

With regards to a functional explanation, it is possible that there are respiratory phase-specific advantages where the brain is best ‘primed’ to receive certain sensory-cognitive information over certain phases. This idea has been explored with regards to the evolutionary and developmental primacy of the olfactory sense and the relationship to its mode of delivery - respiration (Perl et al., 2019). The active sensing of olfaction during inhalation and then the suppression during passive exhalation, could have set a template for subsequently developed non-olfactory sensory processing systems. Further study from this phase-specific perspective is certainly warranted to advance our understanding of respiration’s ongoing influence on sensory processing. However, in the present investigation we take a wider ‘oscillatory’ perspective of entrainment, considering that during each respiratory cycle there would necessitate a shift of cognitive resources, rhythmically primed and unprimed towards the task.

How the respiratory oscillation may interact with cognitive oscillations has formally been proposed by Melnychuk et al., (2018; see also 2021), who considered a coupling of respiration and attention via the locus coeruleus. A few words on the locus coeruleus (LC) and its connection to arousal and attention are warranted here. The LC is the primary site of noradrenaline (NA) production in the brain and has long been recognised for its role in modulating global arousal (Aston-Jones & Bloom, 1981). The LC-NA system is most active during wakefulness and least active during sleep, and acts to modulate the neural gain (i.e., likelihood of firing) of neurons throughout the brain (Poe et al., 2020). More recently, and largely attributed to work by Aston-Jones & Cohen (2005), the role the LC-NA system plays in modulating arousal has been extended to attention. The relationship between arousal and attention is well described by an inverted U-shaped curve, where low LC-NA mediated arousal is associated with drowsy inattentiveness, and high arousal is associated with stimulated distractibility, whereas a moderate arousal state is most conducive for task focus (Aston-Jones & Cohen, 2005b). The LC mediates arousal and attention through its degree of tonic and phasic firing patterns. Oscillations in tonic activity are thought to play a key role in how neural gain is modulated across the brain, and consequently, the relative activation of neural networks (Eldar et al., 2013; T.-H. Lee et al., 2018).

It may be that oscillations in LC tonic activity are somewhat themselves mediated by the respiratory cycle. Melnychuk et al. (2018), cite evidence of the LC's simultaneous role as a key respiratory nucleus, and further, provide their own experimental evidence of a synchronisation between respiration and functional magnetic resonance imaging (fMRI) LC blood-oxygen-level-dependent signal (BOLD) (Melnychuk et al., 2018) as well as pupil diameter (PD) (Melnychuk et al., 2018, 2021) – a commonly used proxy for LC activity (Bang et al., 2023; DiNuzzo et al., 2019; Elman et al., 2017; Joshi et al., 2016; Meissner et al., 2023; Murphy et al., 2014). They reason that respiratory and frontal attentional network oscillations could bidirectionally influence each other via the LC, which could either be conducive or disruptive to focus depending on the coupling relationship at a given time. A recent review on the question of respiratory modulation of PD concluded that more direct testing was needed (Schaefer et al., 2023), however, they do cite several instances of significant effects, and a recent paper from Kluger et al., (2023) provides direct evidence strongly supporting a coupled relationship.

From a cognitive perspective, the oscillatory nature of attention is well represented by Sripada (2018) within an "explore-exploit" model (Sripada, 2018) - "exploitation" being the maintenance of focus on a given task, and "exploration" being a reorientation of attention away from the task in search of alternative objects of focus. The latter is often referred to as 'mind wandering', although this is an emerging field with no consensus on a singular definition (Seli, Kane, et al., 2018) and thus, for clarity, we accepted the overarching term of 'task-unrelated thought' for our purposes. Sripada also outlines the necessity of an "oscillation strategy" between focus and mind wandering, where a balanced approach oscillating between these alternative modes is likely to be the most advantageous, allowing for both exploitative task progression and an explorative break where task unrelated thoughts are generated. Crucially, this oscillation should be of a relatively short time scale since long periods of time in one mode are likely to be detrimental. The driver of such an appropriate balance was suggested by Sripada (2018) as the locus coeruleus (LC).

The LC therefore has a specialised role with regards to arousal and attention, however it is far from being the only brain area propagating respiratory modulated brain oscillations (RMBOs). RMBOs have been observed across subcortical, limbic and cortical areas during cognitive tasks (Kluger et al., 2021; Melnychuk et al., 2018; Nakamura et al., 2022; Perl et al., 2019; Zelano et al., 2016) and during resting, volitional breathing, and attentive breathing conditions (Herrero et al., 2018). Further, theta:beta ratio, an index of attention, synchronises to the respiratory cycle (Melnychuk et al., 2021) and cortico-muscular coherence is modulated by respiratory phase and depth (Kluger & Gross, 2020). RMBOs therefore appear to be a global phenomenon, highlighted by their presence across subcortical and cortical areas and across all major frequency bands at rest (Kluger & Gross, 2021).

RMBOs have recently been contextualised within a predictive coding model as being capable of modulating both the top-down prefrontal cortex predictions generated about the world, and bottom-up sensorimotor information that informs of prediction errors (Brændholt et al., 2023; see also Allen et al., 2023; Boyadzhieva & Kayhan, 2021). This would implicate RMBOs in having an ongoing role in mediating the communication between our inner and outer worlds and even formulating our conscious experience. Specifically, Brændholt et al., (2023) discuss how phase-phase coupling and phase-amplitude coupling of RMBOs to other brain oscillations could modulate the cortical hierarchy of predictions, and additionally, that cortical-wide dynamics could be further influenced by the effect on neural gain from respiratory modulation of the LC. It may be that periods of high attentiveness towards a task may occur when all such coupling pathways are harmonious (rather than negatively interfering), enhancing stability and synchronicity within the brain and between the brain and environment. A distinction between this predictive coding model and Melnychuk et al.'s (2018) 'coupled oscillator' model is that the former suggests that coupling relationships between respiration and brain oscillations are dependent on ongoing and updating predictions and prediction errors, whereas the latter suggests an inherent coupling between the nodes, independent of a predictive process, although still of variable strength.

Presently, we investigated the idea that when respiration entrains to the rhythms of an external task, this may implicate a respiratory-locked cyclic modulation of attention, observed in behaviour and accompanying neural oscillations in the LC and cortical areas. To investigate this, we utilised a paradigm that enabled continuous tracking of behavioural and neural signatures of attention and respiratory oscillations over time. A key aim was to trace the neural dynamics of attentional-respiratory coupling continuously throughout the intervals between overt behaviour (i.e., target responses). The paradigm introduces targets that are defined by a gradual change in a single feature of a continuously presented stimulus to circumvent the exogenous capture of attention by sudden stimulus onsets. In addition, we measured how experiential (experience sampling), states (i.e., reported focus) are modulated over the respiratory cycle, and specifically, with respect to a respiratory-task entrainment window. Within individuals, we hypothesised that our measured attentional indices would be greater during the window of entrainment, and therefore lesser outside of it. Importantly, the approach allows discrete mapping of the respiratory signal to physiological indices of higher cognitive processes (parietal alpha, and frontal theta and delta rhythms), continuous basic sensory processing (SSVEP) and pupil-linked arousal.

As well as considering intraindividual differences in attentional state, we took advantage of recent findings from Moran (2021) who showed that younger adults (YAs) and older adults (OAs) differ in their explore-exploit attention strategy when performing a continuous sustained attention task. YAs appeared to spend more time than OAs in an explorative mind wandering state, tuning in to exploit targets as and when required. In contrast, OAs appeared to maintain a more exploitative focused state, possibly a more risk-averse strategy in the face of age-related decrements in cognitive flexibility. This conclusion was evidenced from differences in experience-sampling reported focus (Moran et al., 2021) as well as properties of target-locked physiological indices of attention (Moran, 2021). Crucially, despite age-related differences in these, task performance between groups was comparable. Therefore, in the present study we examined respiratory-attentional coupling as a function of age given different explore-exploit strategies that characterise YAs and OAs. Since OAs seem to maintain higher top-down control towards the task in their more exploitative attentional strategy, we reasoned that their respiratory cycle should be more strongly entrained to the task than YAs, given the link between the respiratory and attentional-arousal systems outlined above.

Accordingly, the OAs should show more pronounced respiratory modulation of attentional indices.

Methods

Participants

In total, 43 OAs and 42 YAs participated in the study (n = 85). OAs were aged between 65 and 80 years, YAs were between 18 and 35. Otherwise, inclusion criteria were: no personal or family history of epilepsy, no personal or family history of unexplained fainting, no sensitivity to flickering light, no personal neurological or psychiatric illness or brain injury, normal or corrected-to-normal vision. A further requirement for OAs was a passing score of 24 on the Montreal Cognitive Assessment (MoCA; Nasreddine et al., 2005). OAs were recruited from a research participant panel, and YAs were largely students at Trinity College, recruited through college communications. Sessions lasted 2-3 hours and participants were reimbursed for their time with a €40 voucher.

Eight participants were excluded due to incomplete data collection and a further five for low hit rate (>3 standard deviations from the mean). This resulted in OAs n = 34, YAs n = 38 for the respiratory analysis. Ten participants were excluded from this sample for the EEG analyses due to excessive noisy channels and/or high number of trials excluded during artifact rejection, OAs n = 29, YAs n = 33. Five OAs participants were excluded from the sample for the PD analysis, OAs n = 29, YAs n = 38, however many additional whole blocks and trials had to be excluded due to poor quality recordings, particularly in the OAs group. This resulted in an average of 314 (out of 384) trials included in the PD analysis per OAs participant, and 340 trials for the YAs. The OAs group posed some difficulty recording due to partial eyelid occlusion.

Procedure

Participants were tested at Trinity College Dublin. Following briefing and consent they were fitted with the EEG and respiratory belt set up, OAs filled in the Montreal Cognitive Assessment, both groups were given instructions for the GradCCD-ES task (see next section), and they performed said task for 8 blocks, approximately 8 min each. Additionally, all participants filled out pre- and post- task subjective state questionnaires which are not reported here.

Gradual Contrast Change Detection with Experience Sampling (GradCCD-ES) Task

Participants performed the GradCCD-ES task on a 40cm cathode-ray tube presentation monitor in a sound-attenuated room with no lighting except the monitor. Participants sat at a distance of approximately 57cm from the monitor, with their head supported by a chinrest to minimize head and eye movements. The monitor was set to a 100Hz refresh rate and resolution of 1024x768. The task was hosted on MATLAB 2016b using the Psychtoolbox-3 toolbox (Brainard, 1997). Prior to the task, participants were given verbal and visual task instructions as well as information on 'Mind Wandering', as they were required to indicate during the task whether they were 'focused on the task', or 'mind wandering' (experiencing task-unrelated thoughts). They additionally performed a short practice round with the experimenter in the room, to demonstrate features of the task and assess comprehension.

During the GradCCD-ES task (McGovern et al., 2018; Moran, 2021; Moran et al., 2021; O'Connell et al., 2012) participants fixated on the center of the centrally presented, black and white, checkerboard annulus stimulus (outer radius = 8°, inner radius = 3°) displayed on a grey background. The stimulus flickered on and off at a frequency of 25 Hz, to induce a steady-state visually evoked potential (SSVEP) observable in the EEG over occipital areas at the same frequency. This served as a continuous signal indicating sensory encoding of the stimulus (O'Connell et al., 2012). The target to be identified in the task was a gradual decrease in stimulus contrast (65% to 35% over 1.6 s), which then returned to its original contrast (over 0.8 s). Participants were instructed to respond with a mouse click (right hand) as soon as they noticed this target. Targets occurred after variable inter-target intervals of 3, 5, and 7 s, occurring 16 times each (48 total targets), with the order shuffled randomly within each block. Additionally, the stimulus presentation was interrupted by similarly variably presented ‘thought probes’ (TPs). Here, the stimulus was taken off-screen for 500 ms and replaced with text stating: “Choose the response that best describes your [their] mental state right before this screen appeared. [1] Focused on the task, [2] Unintentionally lost focus on the task, or [3] Intentionally disengaged from the task. The intentionality of mind wandering (responses ‘2’ and ‘3’) was of interest to Moran (2021), who followed Seli et al., (2015), and we preserved the paradigm for replication purposes, however the intentionality was not of interest to the current investigation. Thus, these responses are combined into just ‘mind wandering’. Participants responded with their perceived attentional state immediately prior to the TP presentation with a keyboard press of ‘1’, ‘2’ or ‘3’ (right hand). Each block consisted of 48 targets, 16 TPs, and lasted ~8 mins each. Participants performed 8 blocks in the session and were offered short breaks in between every block.

From participant responses we derived: i) Mean reaction time (RTm; time period between target presentation and participant response), ii) Coefficient of variation of RT (RT CoV; standard deviation of RT divided by RTm), iii) Hit rate (proportion of identified targets), iv) False alarms; clicks outside of target presentation time), and v) Focus/mind wandering (proportion of TP responses indicated). Each behavioural variable was averaged after collapsing across the blocks, and Focus/mind wandering counts were averaged across the blocks.

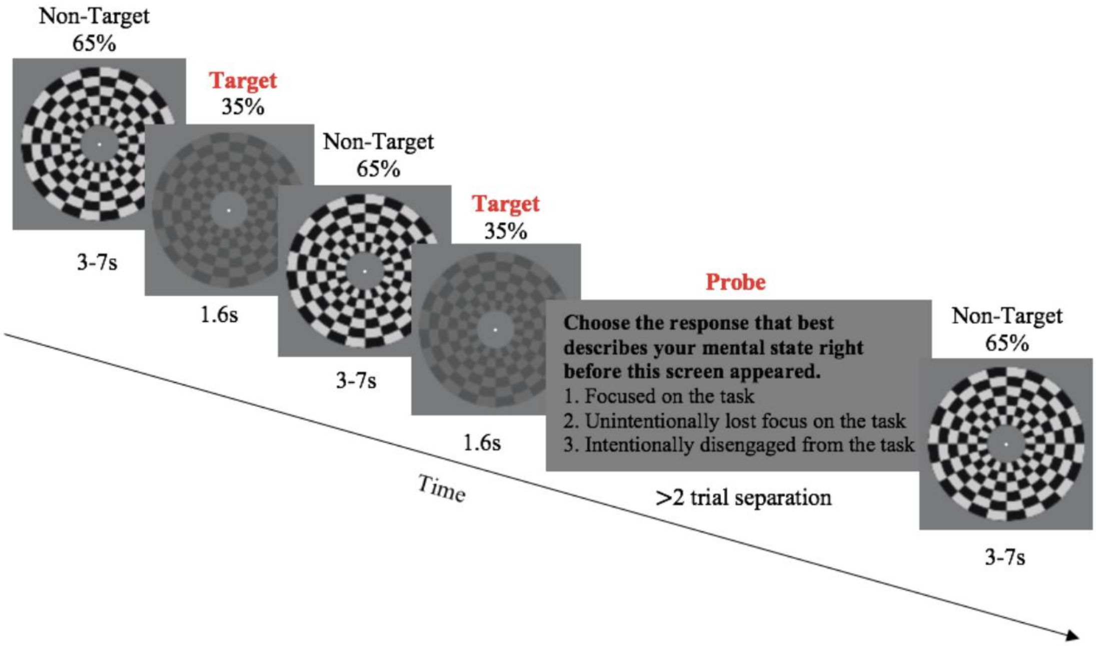


Figure 2.1 - Task schematic of the Gradual Contrast Change Detection with Experience Sampling (GradCCD-ES) Task. A continuously presented checkerboard, anulus stimulus decreases in contrast after variable intervals which is the target to be identified by participants, who respond with a mouse click upon recognition. Additionally, the stimulus is interrupted with experience-sampling thought probes (TPs) which ask the participant to categorise their attentional state immediately prior to the TP presentation. Each block consists of 48 targets, 16 TPs and lasts approximately 8 mins each. A testing session consisted of 8 blocks.

Pupillometry Acquisition and Preprocessing

Pupil diameter (PD) was collected using Eyelink 1000 SR Research camera and associated software from the left eye at 1000 Hz. Participants were instructed to maintain their head on a chinrest to minimise pupil detection loss. A calibration and validation check was performed before each block.

Data was preprocessed using custom made MATLAB scripts. For blink detection, the blink indices provided by the Eyelink automatic detection were extended 50 ms either side. These periods were removed and interpolated linearly. Blink/interpolated sample points within a recording session were saved and used for trial rejection in subsequent analyses, excluding trial windows that contained >30% blink/interpolated samples. PD was then low pass filtered using a zero-phase digital Butterworth filter with cut-off frequency 4 Hz and filter order 4, and linearly detrended.

Target-locked analysis: PD was normalised for each block; trials windows were extracted separately for 2000 ms pre-target and 4000 ms post-target periods and were checked for number of blink/interpolated samples. Valid windows were corrected by subtracting the mean value 200 ms pre-target for pre-target windows (end corrected) or post-target for post-target windows (baseline corrected).

Normalised PD for the block was also used for 'Variables over the respiratory cycle analysis' – see subsequent section.

EEG Acquisition and Preprocessing

Acquisition and preprocessing: EEG signal was collected using Biosemi equipment and software with 128 scalp electrodes plus two electrooculogram electrodes (above and below the left eye) recorded at 256 Hz. Data was preprocessed using custom made MATLAB scripts and FieldTrip toolbox (Oostenveld et al., 2010). Data was detrended, band-pass filtered at 0.2 - 40 Hz, with two pass method and hamming window, and re-referenced using global average. Analyses involving beta frequency were also band-stop filtered at 23 – 27 Hz to exclude the 25 Hz stimulus flicker. Channels deemed to have excessive variance by visual inspection were removed and interpolated using spherical spline method. Participants with number of interpolated channels >10% were excluded.

Target-locked preprocessing: For generating target-locked neural indices, EEG data was extracted -250 ms to 2000 ms with respect to target presentation for the post-target centro-parietal positivity (CPP), steady-state visually evoked potential (SSVEP; 25 Hz) and left hemisphere beta (LHB; 8 – 30 Hz). Trial windows were -2000 ms to 0 ms relative to target for pre-target alpha. Trials were baseline corrected by subtracting the mean within the first 250 ms period. Each trial was subject to artifact detection using thresholds of 250µV for eye electrodes (upper minus lower), and 100µV for scalp electrodes, rejecting all trials where any values exceeded these values. Miss trials were also excluded. Finally, current source density was performed to increase spatial resolution (Kayser & Tenke, 2015).

Frequency-power preprocessing: For the subsequently described '*Variables over the respiratory cycle analysis*', EEG power in delta (1-4 Hz), theta (4-7 Hz), alpha (8-14 Hz), and SSVEP (25 Hz) frequency bands were analysed. EEG data for this was subject to the same above preprocessing steps prior to trial segmentation. Frequency-power across each block was calculated using Short-Time Fourier Transform, window size 1 s with 20% overlap, which was then z-score normalised. The corresponding median respiratory phase angle within each window was additionally extracted. Channels chosen for each frequency band were determined from grand average population mean topographic plots as those showing the highest power. Delta and theta channels: FP1, FP2, FPz; alpha channels: P07, P7, P8; SSVEP channels: PO4, PO7 (See Figure S2.5).

EEG Target-Locked Neural Indices Analysis

CPP: Trials were averaged for each participant at channel A4 and then across participants in each group to generate the CPPs. Group average topographic plots -150 to -50 ms relative to target response showed a widespread area of positivity which varied between participants and thus CPz was chosen to be consistent with Moran (2021). CPP slope was calculated for a linear best fit line 250 to 750 ms of the participants mean post-target. CPP peak was the maximum value of the participant mean 500 to 1750 ms post-target. Latency was the timepoint post-target of the CPP peak. For plotting, CPPs were low-pass filtered using a zero-phase digital Butterworth filter with cutoff frequency 8 Hz and filter order 4. The CPP onset latency plotted was calculated using a running t-test and determined as the first sample point to significantly deviate from 0 in a positive direction.

SSVEP: Channel selection for the SSVEP was determined by signal to noise ratio group average topographic plots of the power at 25 Hz divided by the mean power of neighboring frequencies of the fast Fourier transform), 23 and 27 Hz. Highest power was observed for OAs at POz, and YAs at PO4. For each trial, a Short-Time Fourier Transform of 400 ms window size (8 cycles of SSVEP) and 20 ms step size was applied, which were then averaged for each participant. Participant means were baseline normalised by dividing by the mean value in the first 250 ms. SSVEP slope was calculated for a linear best fit line 350 to 850 ms of the participant mean post-target. SSVEP amplitude was calculated as the mean value 500 to 1600 ms of the participant mean post-target.

LHB: Channel selection for the LHB was determined from group average topographic plots as the electrode with the minimum power -100 ms to 100 ms relative to target response – C3 for both groups. For each trial, a Short-Time Fourier Transform of 400 ms window size and 20 ms step size was applied, which were then averaged for each participant. Participant means were baseline normalised by dividing by the mean value in the first 250 ms. LHB slope was calculated for a linear best fit line 350 to 850 ms of the participant mean post-target. An additional LHB Slope variable was determined around the time of mean RT, in the window 1000 to 1300 ms post-target. LHB amplitude was calculated as the mean value 500 to 1250 ms of the participant mean post-target.

Respiration Acquisition and Preprocessing

Recording and preprocessing: Respiratory signal was collected using a SleepSense respiratory effort sensor belt, recorded at 256 Hz via a Biosemi Amplifier and Biosemi Actiview software. Data was preprocessed using custom made MATLAB scripts. Signals were first inspected by eye for poor recording sessions and then were low pass filtered using a zero-phase digital Butterworth filter with cutoff frequency 0.6 Hz and filter order 4. Finally, filtered signals were then linearly detrended.

Respiratory Entrainment Analysis

Preprocessed respiratory signal for the block was Hilbert transformed and the phase angles in radians were extracted at the times of task events – target presentation, target response, TP presentation, TP response. These event-locked phase angles were collapsed across all blocks and tested against the null hypothesis of uniformity with a Rayleigh’s test. The resultant vector length of respiratory phase angles was the primary measure of entrainment as well as the mean angle it tended towards. Circular statistics were performed using CircStat toolbox (Berens, 2009b). See Cremers & Klugkist (2018) for more information on calculating circular statistics.

Variables Over the Respiratory Cycle Analysis

To test for a modulation of variables over the respiratory cycle, participant-grand averaged variables of interest were z-score normalised and averaged within a moving phase window across the cycle. For RTm and Focus report %: phase window length = π/4, window overlap = 90%. For delta, theta, alpha and SSVEP power (see section *EEG frequency-power analysis*): phase window length = π/36, window overlap = 75%; PD: phase window length = π/36, window overlap = 75%. The relatively small windows in the physiological compared to the behavioural variables were afforded due to the richness of data available for these continuous, non-task event locked indices. To determine the significance of variable means within any given respiratory phase bin, one-sample permutation testing was used: for each phase bin, the corresponding normalised actual values were permuted 1000 times, such that in each permuted distribution they were randomly attributed positive and negative signs, and the mean was taken. The corresponding p value for each phase bin was calculated as the percentage of permuted means that were higher or lower than ± actual phase bin mean. The corresponding t statistic was the actual phase bin mean minus the mean of permuted means, over the standard error of the mean (SEM) of the actual phase bin. Statistical significance was determined at the $p = 0.05$ level for all variables.

Results

Age group differences in behavioural, experiential, and physiological signatures of attention

See Appendix 2.1 for the full analysis of testing for attentional differences between age groups. This was not a primary finding of the present study but rather a manipulation check to utilise the age groups as a group difference in attentional strategy. Taken together, our findings of significant age-related differences of higher reported focus, higher pre-target alpha variation, lower post-target steady-state visually evoked potential slope, and higher post-target pupil diameter, indicate that the OAs had higher attentiveness towards the task than the YAs drawing the same conclusion as Moran (2021). For the neural index's statistics and plots, we ensured that a sufficient number of trials were included for each participant, to contribute to a high signal-to-noise ratio (Table S2.4).

Respiratory-Task Event Entrainment

The distribution of respiratory phase angles at the time of task events - target presentation, target response, TP presentation, TP response - collapsed across all blocks was our indicator of respiratory-task event entrainment.

The percentage of participants who rejected the Rayleigh test null hypothesis of uniformity around the respiratory cycle were as follows: target presentation: OAs $M = 60\%$, YAs $M = 70\%$; target response: OAs $M = 80\%$, YAs $M = 68\%$; TP presentation: OAs $M = 57\%$, YAs $M = 41\%$; TP response: OAs $M = 86\%$, YAs $M = 57\%$ (Figure 2.2). It was therefore a majority group finding (bar YAs TP presentation), but not a ubiquitous one.

The primary measure of respiratory-task event entrainment was the resultant vector length (VL) of respiratory phase angle distributions. A higher VL indicates lower variability in phase angles. OAs had significantly higher VLs for: target response, OAs $M = 0.20 \pm 0.02$, YAs $M = 0.13 \pm 0.01$, $t(70) = 3.20$, $p = 0.002$, $d = 0.75$; TP presentation, OAs $M = 0.18 \pm 0.02$, YAs $M = 0.13 \pm 0.01$, $t(55.8) = 2.42$, $= 0.019$, $d = 0.58$; and TP response, OAs $M = 0.45 \pm 0.04$, YAs $M = 0.24 \pm 0.03$, $U = 982$, $p < 0.001$, $r = 0.52$; but not target presentation, OAs $M = 0.14 \pm 0.01$, YAs $M = 0.12 \pm 0.01$, $t(70) = 1.22$, $p = 0.228$ (Table 2.1).

We also tested whether these VLs significantly changed over the 8 blocks, which they did not (Figure S2.3).

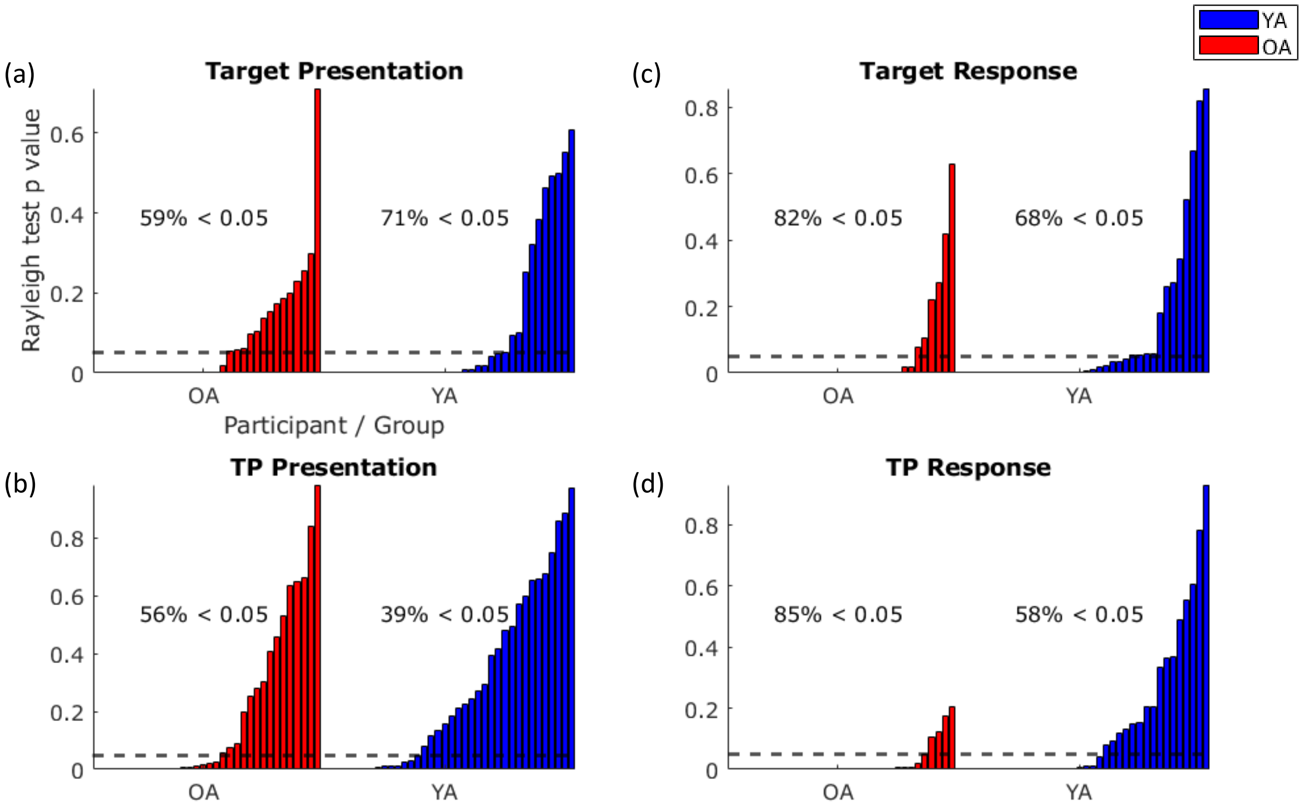


Figure 2.2 - Bar graphs of *p* values returned for each participant from Rayleigh tests against a null hypothesis of uniformity for respiratory phase angles at the times of (a) target presentation, (b) target response, (c) thought probe (TP) presentation, and (d) TP response. YAs in blue, OAs in red. Values displayed on graphs indicate the percentage of participants in each group that showed significant ($p < 0.05$) non-uniformity. Significant non-uniformity was a majority group finding (except YAs TP presentation), but not a ubiquitous one.

The mean angles of respiratory entrainment encompassed the exhale-inhale transition (Figure 2.3). Target presentation, target response and TP presentation respiratory phase angles were majorly on the late exhale side, while TP response tended towards the early inhale. Entrainment of any task event to late inhale was almost absent. OAs mean entrainment angles were earlier in the cycle, this was only statistically significant (Watson-Williams test; circular T-test) for TP presentation, *F*(70) = 9.04, *p* = 0.004, but target response *F*(70) = 3.76, *p* = 0.06 was not far from significance.

We used this analysis to define an approximate entrainment window from the latter half of exhalation to the first quarter of inhalation. Despite encompassing roughly a third of the cycle (37.5%), this window contained a substantial proportion of the participant-mean respiratory phase angles: 85% of target presentation, 86% of target response, 84% of TP presentation, and 88% of TP response.

It is worth noting also that we tested the hypothesis that respiratory entrainment correlates with task performance or reported focus, however, VLs were not significantly correlated to any task variable while covarying for age. Additionally, we tested to see if there was a significant change in VLs over the blocks, however there was no significant main effect of blocks or interaction for any (Figure S2.3).

Respiratory-Task Event Vector Lengths (VL)

Independent Samples T-Test

	t	**df**	***p***	**Cohen's *d***
Target Presentation VL	1.215	70	0.228	0.287
Target Response VL	3.188	70	**0.002**	0.753
TP Presentation VL[a]	2.423	55.8	**0.019**	0.578

Mann Whitney-U Test

	U	***p***	**Rank-Biserial Correlation**
TP Response VL	982	**< 0.001**	0.520

Table 2.1 – Results from means comparisons tests between age groups, OAs and YAs, testing for differences in respiratory-task event vector lengths (VL). OAs had significantly higher VLs for target response, thought probe (TP) presentation ($p < 0.05$), and TP response ($p < 0.001$), but not target presentation, ($p > 0.05$).

[a] *Welch's T-Test*

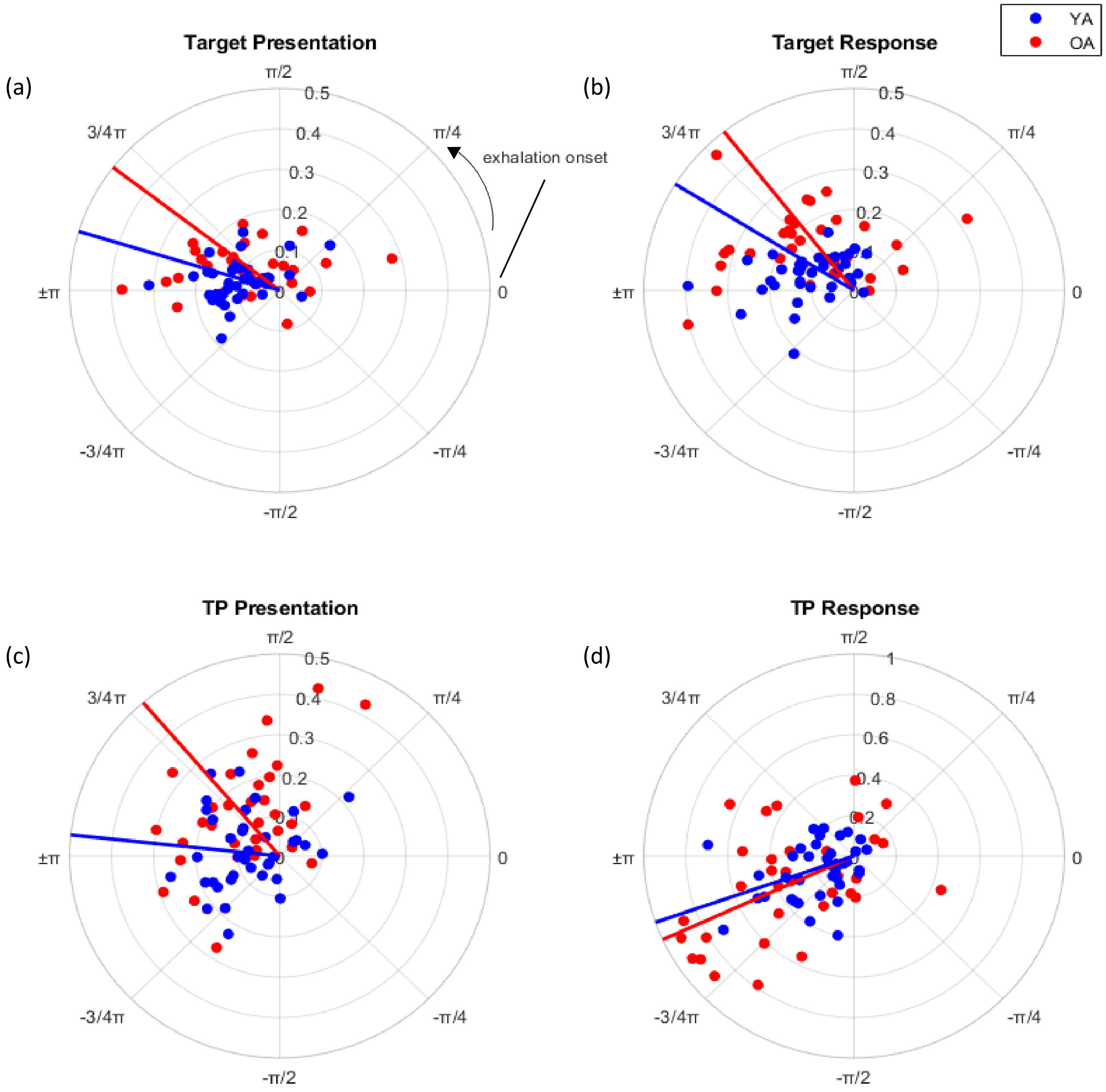


Figure 2.3 - Polar scatter graphs of the mean resultant vector lengths (VLs; radial axis) and respiratory phase angles (angular axis in radians), indicating the strength and angle of respiratory-task event entrainment respectively. Dots represent participant means and solid lines represent the group mean angles, YAs in blue, OAs in red. 0 radians represents exhalation onset and the respiratory cycle proceeds anti-clockwise. The majority of respiratory phase angles occurred between mid-exhalation and early inhalation for (a) target presentation, (b) target response and (c) thought probe (TP) presentation. (d) TP response showed a tighter clustering around early inhalation. OAs mean angles were significantly earlier in the respiratory cycle vs YAs for (c) TP presentation (*p* = 0.004), and (b) target response showed trending significance (*p* = 0.06).

Behavioural, Experiential and Physiological Indices Over the Respiratory Cycle

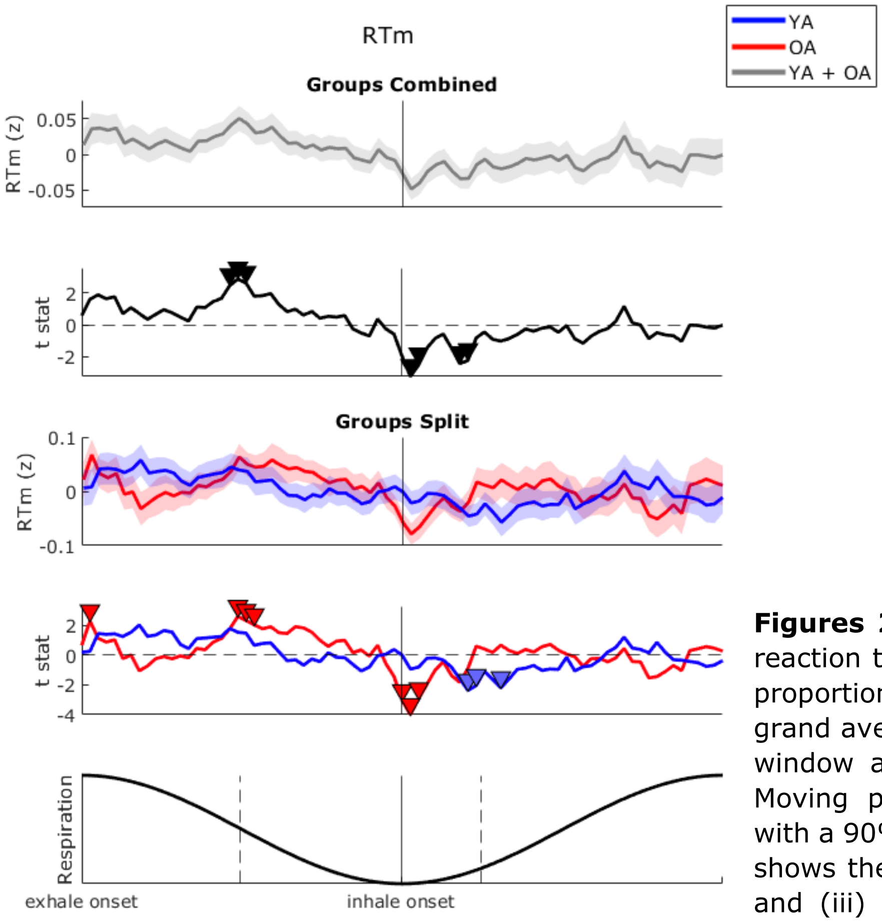
Respiratory entrainment to the times of target presentation, target response and TP presentation, was evident within an approximate window from the latter half of exhale to the first quarter of inhale. We therefore sought to investigate a ‘mapping’ of the respiratory cycle in terms of average behavioural, PD, and electrophysiological indices of focus, particularly with regards this entrainment window. Means within each respiratory phase bin were tested for being significantly different from 0 using one-sample permutation testing. To investigate the influence of entrainment, we additionally analysed significant target entrainers, and non-significant target entrainers, separately for each group. Note, we chose target presentation entrainment as it did not differ between age groups and also gave the closest 50/50 split. However, sample sizes were not even, with the behavioural analysis containing 47 entrainers, vs 25 non-entrainers, PD analysis 46 vs 21, and EEG analysis 45 vs 24.

Behavioural and experiential indices: RTm was significantly quicker just after inhale onset for both groups, and significantly slower at phases in exhalation for the OAs (Figure 2.4a). This pattern was well maintained within the entrainers, but almost abolished in the non-entrainers (Figure 2.4c). OAs reported significantly more focus during early inhale and less during mid exhale and mid inhale. YAs also reported lower focus during mid inhale (Figure 2.4b). This pattern for Focus was well maintained in the entrainers, with an additional period of higher Focus in early exhalation for the YAs. In the non-entrainers, only OAs showed resemblance of this pattern (Figure 2.4d).

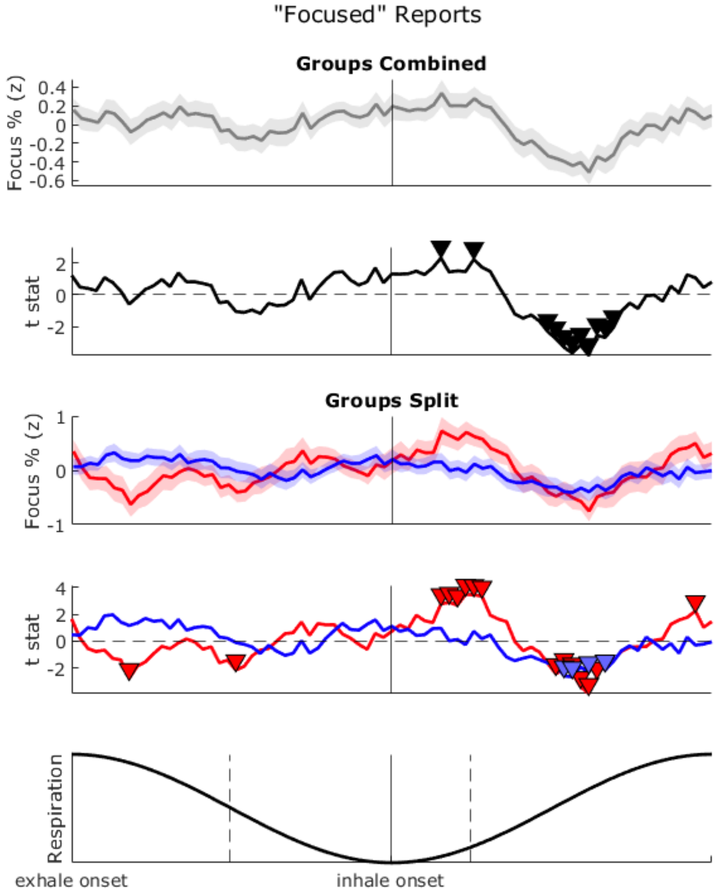
PD: PD showed a significant peak across the last quarter of exhalation and a trough over mid inhalation, which was largely driven by differences in OAs (Figure 2.5). The trough over inhalation was maintained in the OAs entrainers. In the non-entrainers there are signs of significantly different phases, but the pattern is abolished when splitting into age groups (Figure 2.5)

Electrophysiological indices: Frontal delta, theta and occipital alpha all show a similar pattern, being significantly lower from the final phase of inhale into early to late exhale, and higher during early to mid inhale (Figure 2.6). This pattern was more distinct for OAs, who showed a greater amplitude in their fluctuation. In contrast, the SSVEP more significantly modulated by the YAs, being significantly higher from late inhalation, partially continuing through most of exhalation, and lower in early-mid inhalation. OAs partially followed the pattern over inhalation (Figure 2.6). The patterns were well maintained in the entrainers, and fairly well in the non-entrainers with a few notable differences. The delta, theta, and alpha peaks were flatter, broader, and earlier, and the YAs alpha, and OAs SSVEP patterns were considerably different.

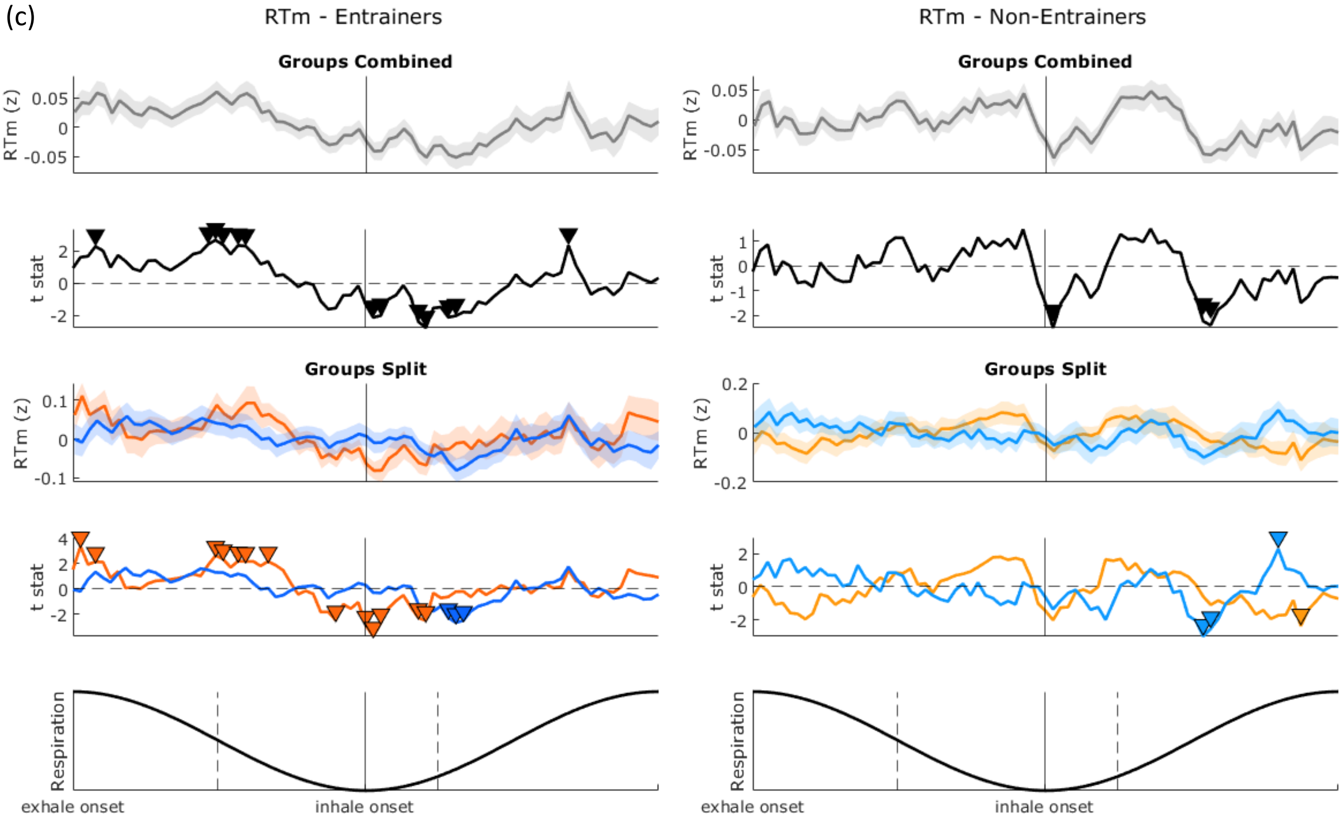
(a)



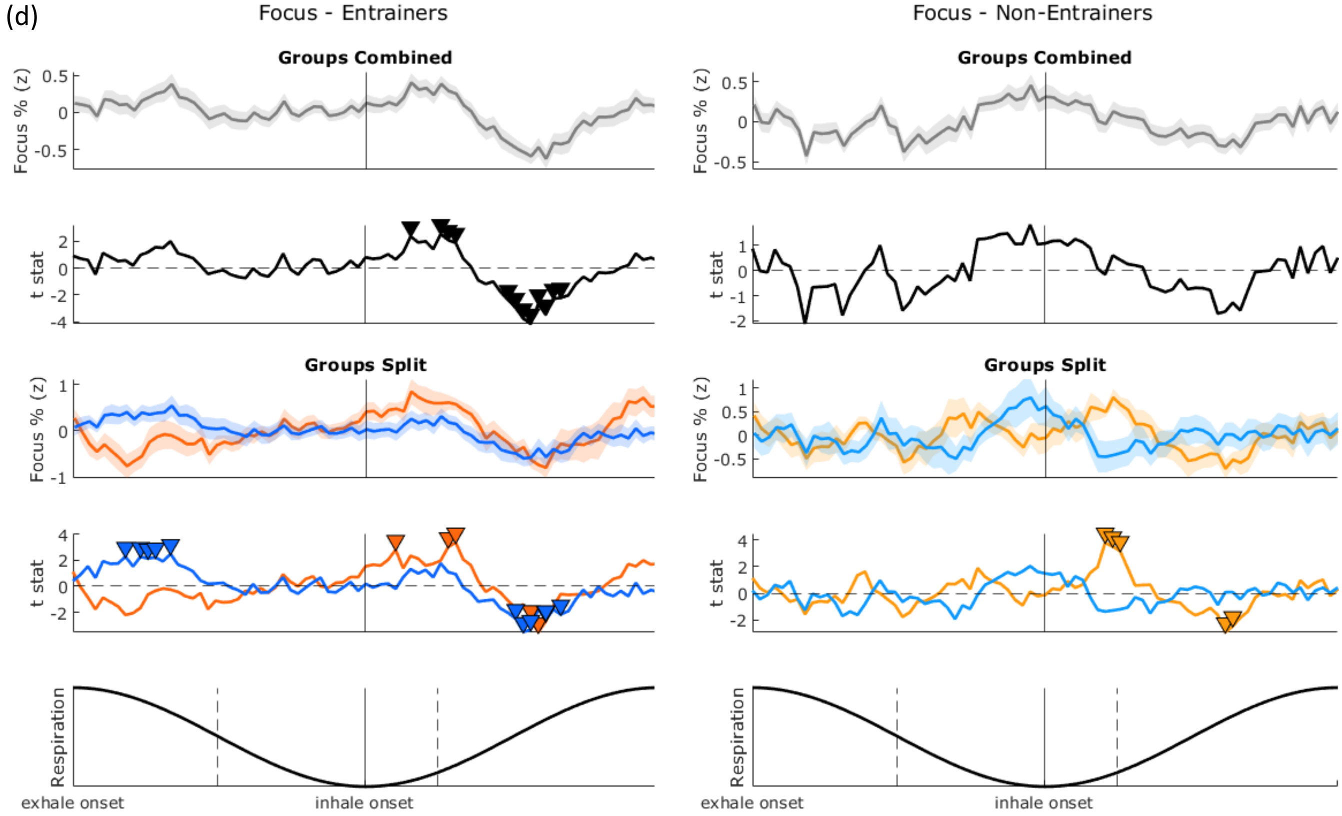
(b)



Figures 2.4a and 2.4b - Normalised reaction time mean (RTm) (a) and the proportion of 'Focused' reports (b) were grand averaged within a moving phase window around the respiratory cycle. Moving phase window of length п/4 with a 90% overlap. For (a) and (b), (i) shows the resultant plot for all (black) and (iii) shows the groups split, YAs (blue) and OAs (red) - shaded area represents the standard error of the mean; vertical solid black line indicates inhalation onset. Graphs (ii) and (iv) plot the *t* statistic resulting from one-sample permutation testing against 1000 sets of simulation data. Arrows indicate significant ($p < 0.05$) phase bins. (v) shows the respiratory waveform for reference. Dashed vertical lines represent the approximate 'entrainment window' defined by our observations.



Figures 2.4c and 2.4d - Same as 6a and 6b but split into entrainers (left) and non-entrainers (right). OAs in reds and YAs in blues.



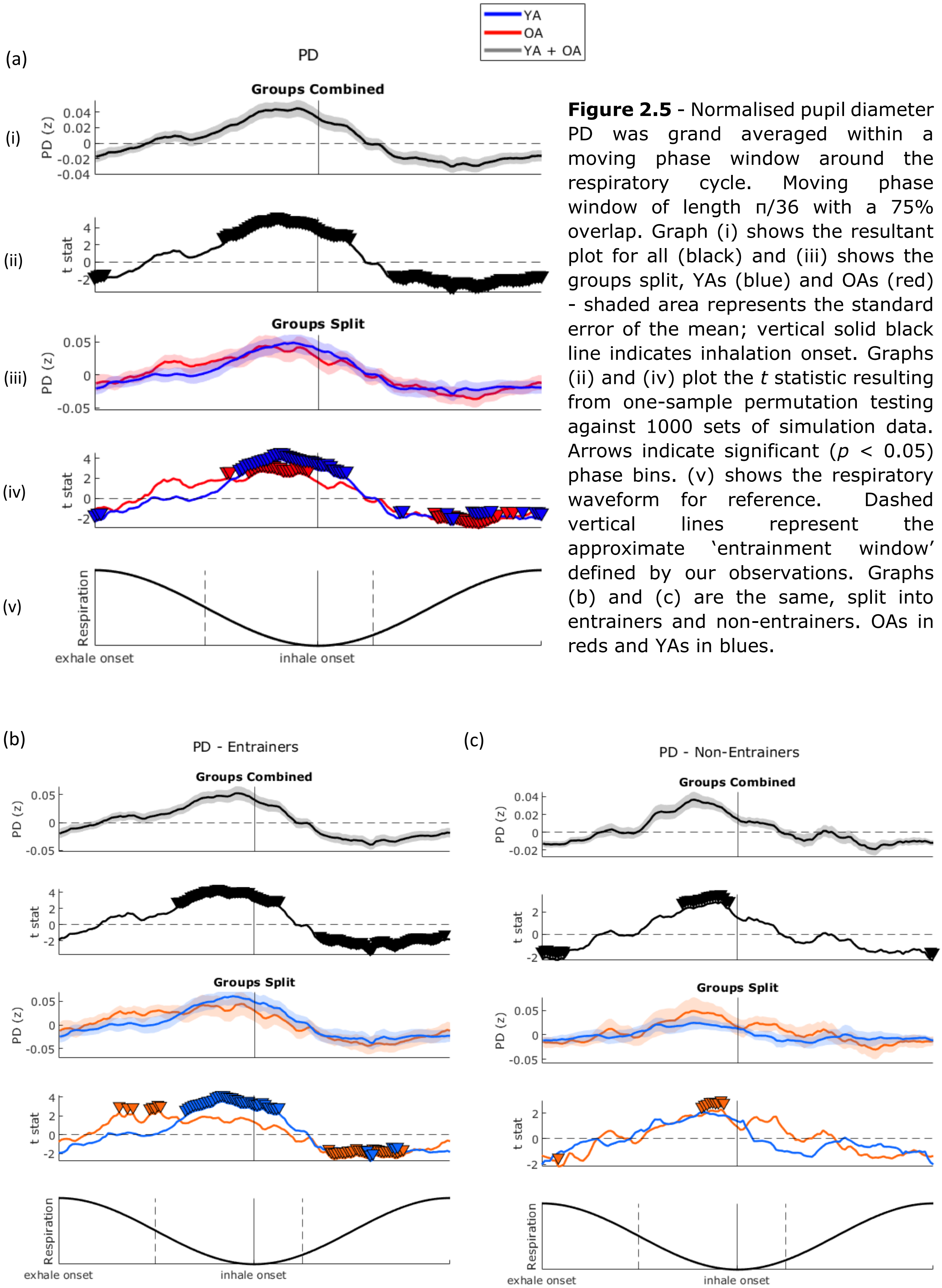


Figure 2.5 - Normalised pupil diameter PD was grand averaged within a moving phase window around the respiratory cycle. Moving phase window of length π/36 with a 75% overlap. Graph (i) shows the resultant plot for all (black) and (iii) shows the groups split, YAs (blue) and OAs (red) - shaded area represents the standard error of the mean; vertical solid black line indicates inhalation onset. Graphs (ii) and (iv) plot the *t* statistic resulting from one-sample permutation testing against 1000 sets of simulation data. Arrows indicate significant ($p < 0.05$) phase bins. (v) shows the respiratory waveform for reference. Dashed vertical lines represent the approximate 'entrainment window' defined by our observations. Graphs (b) and (c) are the same, split into entrainers and non-entrainers. OAs in reds and YAs in blues.

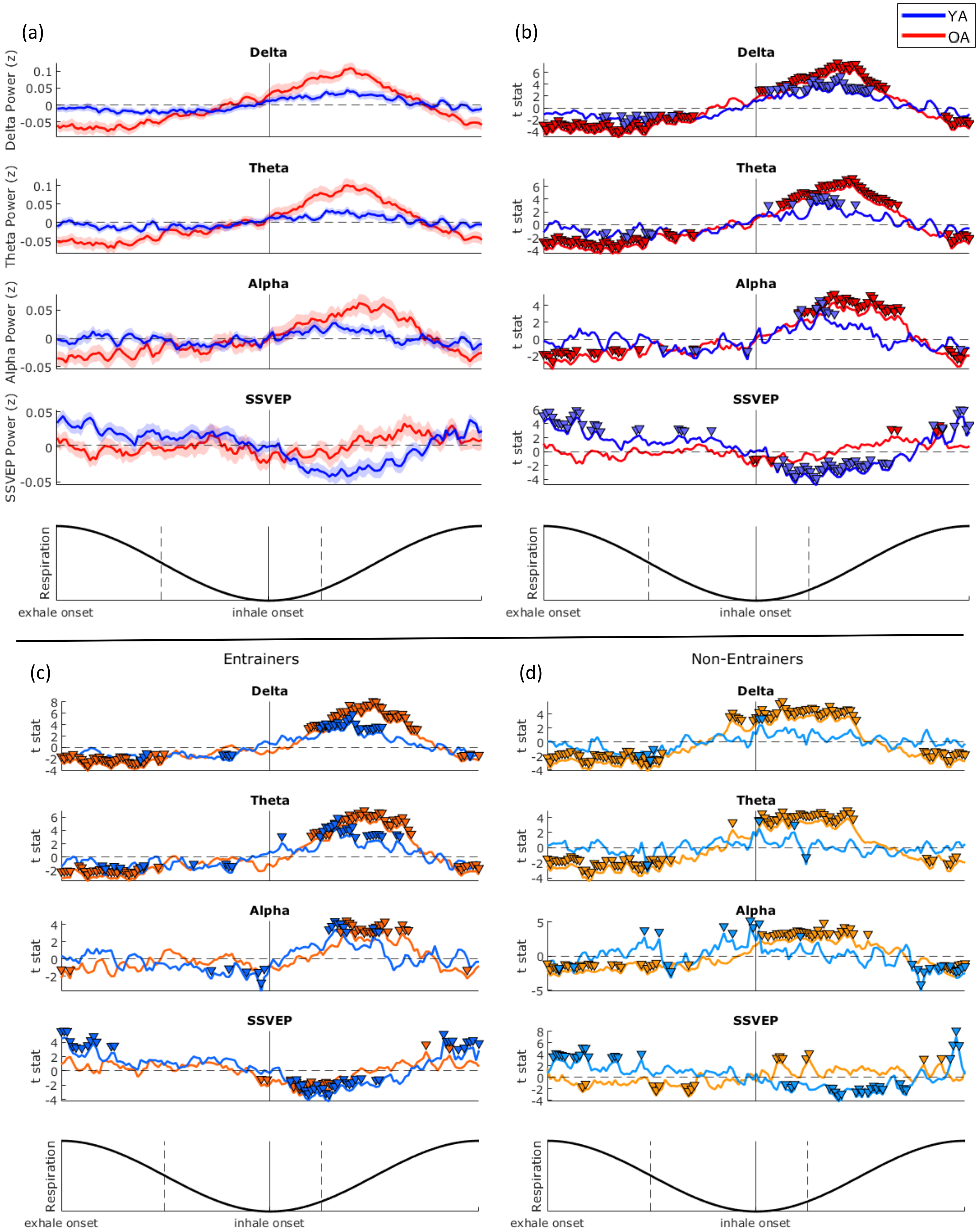


Figure 2.6 - Normalised frontal delta and theta, and occipital alpha and SSVEP power, were grand averaged within a moving phase window around the respiratory cycle. Moving phase window of length π/36 with a 75% overlap. (a) shows the resultant plot for each group, YAs (blue) and OAs (red); shaded area represents the standard error of the mean; vertical solid black line indicates inhalation onset. (b) shows the plotted *t* statistic resulting from one-sample permutation testing against 1000 sets of simulation data. Arrows indicate significant ($p < 0.05$) phase bins. Bottom graphs show the respiratory waveform for reference. Dashed vertical lines represents the approximate 'entrainment window' defined by our observations. (c) and (d) show the t statistics split by entrainers and non-entrainers. OAs in reds and YAs in blues.

Discussion

In the present study we observed significant entrainment of respiratory phase to events in a sustained attention task, with OAs entraining more strongly than YAs. Additionally, we report significant modulation of behavioural, physiological, and, for the first time, experiential indices of attention over the respiratory cycle, the degree of which was greater in OAs for most indices but was also partially driven by significant respiratory-task entrainment.

Our groups of YAs and OAs were intended to naturally divide differing attentional strategies applied to the task. Our sample of OAs responded to thought probes with significantly more “Focus” reports than the YAs, which is consistent with the previous study to use this task (Moran, 2021) and is a robust finding in this area of research generally (Diede et al., 2022; Jackson & Balota, 2012; Maillet & Schacter, 2016; Robison et al., 2022). In complement to higher Focus reports, and also consistent with Moran (2021), the OAs showed differences in target-locked physiological indices which all indicate that the OAs had a more ‘exploitative’ attentional strategy than the YAs. The OAs appeared to encode the target evolution more reliably (SSVEP), show a stronger motor preparation prior to response (LHB), exhibit lower variation in pre-target posterior alpha (strongly related to visual processing and attention; Clayton et al., 2018), and demonstrate a greater evoked pupil diameter (PD) response to targets. This contrasts with the YAs, who exhibited signs of spending more time in an ‘explorative’ mode, letting the mind wander in between task events and tuning into the task as and when required.

We extend these age-related differences to show that the OAs also entrained their respiration more strongly to the times of target response, TP presentation, and TP response. Whilst respiratory-task entrainment has been reported across many tasks (Grund et al., 2022; Huijbers et al., 2014; Johannknecht & Kayser, 2022; Melnychuk et al., 2018; Park et al., 2020; Perl et al., 2019) there is still little understanding as to which individuals are likely to entrain. Our age-related difference implies that the attentional strategy applied to the task could be a contributing factor, especially since our groups did not differ in task performance.

We additionally found some intriguing effects of how a range of attentional indices are modulated over the respiratory cycle. Not only were we able to analyse age-related differences here, but we could further split these groups into those that did, and did not, show significant target entrainment. Utilising these findings as the focus of the discussion, we attempt to characterise the roles that attentional strategy and respiratory entrainment may play in a respiration-attention relationship.

We should note a few important caveats at this point. Firstly, it is recognised that the sample size for the non-entrainers is considerably smaller than the entrainers for all attentional indices, and thus interpretations should be made with this in mind. Additionally, caution is warranted when comparing effects at specific respiratory phases across any of the measures as they are generalisations across all respiratory cycles, and the changes are not necessarily co-occurring every cycle. Finally, it is worth noting that the physiological measures (PD and EEG power) were continuously monitored signals, in contrast to the task event-locked measures (RTm and Focus) where each respiratory phase bin had an average of only 12-20 counts per participant to analyse (Figure S2.2). This means that the task-locked modulation statistics had comparatively much less power.

We first consider how PD is modulated across the respiratory cycle as this relates to a prominent model for respiration-attention coupling via the locus coeruleus (LC). As outlined by Melnychuk et al., (2018), the LC plays vital functions in both attention and respiration processes. Our PD measures were intended as an LC activity proxy (Bang et al., 2023; DiNuzzo et al., 2019; Elman et al., 2017; Meissner et al., 2023; Murphy et al., 2014)..

Observing the PD pattern with both groups combined, entrainers and non-entrainers, it is clear that there is a significant modulation of PD by respiratory phase, supporting previous positive findings (Schaefer et al., 2023). Both age groups showed similar modulation patterns, with a significant increase in PD towards the end of exhalation, and a significant decrease over mid-late inhalation. It appears as though the entrainers in each age group were largely driving the modulation pattern, although the OAs non-entrainers did still show the significant increase in late exhalation. It also appears that within the entrainers, the PD increase was more significant for the YAs entrainers, and the decrease for the OAs entrainers.

The fact that the OAs showed some significant modulation of PD regardless of entrainment may speak to an effect of more stable top-down applied attention on stabilising LC tonic fluctuations, particularly through descending control from the anterior cingulate cortex and orbitofrontal cortex (Aston-Jones & Cohen, 2005b). However, a greater influence on PD modulation appears to be respiratory-task entrainment. Entraining the respiratory rhythm to the rhythm of the task, may also have an effect of stabilising LC oscillatory activity, likely registered via input from the pre-Bötzinger complex (Yackle et al., 2017). It is uncertain whether there is a direction of causality here, but it can at least be said that the LC is receiving top-down attentional, and bottom-up respiratory information regarding the rhythms of the task, and this should lead to a stabilisation of tonic LC rhythms, and we believe this is evidenced by a stable cycle-to-cycle PD pattern.

The different PD modulation patterns exhibited by the OAs and YAs entrainers may be telling of their different attentional strategies. We speculate how these patterns could be conducive for cyclic target detection, considering the LC-noradrenaline inverted-U shape relationship with arousal and attention (Aston-Jones & Cohen, 2005b). The increased PD over exhalation may reflect an arousal boost associated with target expectancy, and this appears to be an anticipatory action by the OAs prior to the entrainment period, whereas it occurs over the entrainment window in YAs. Then, the decreased PD during inhalation could reflect a post-target ‘attentional break’ from the task. This appears to be more prominent for the OAs than the YAs. In the attentional literature, both increases and decreases in PD are related to mind wandering, with the latter particularly characterised by low arousal, inattentiveness (Unsworth & Robison, 2016, 2018) which would be fitting for such a proposed attentional break where targets are less expected. Importantly, this is not to say that participants were mind wandering at this phase in every respiratory cycle, but rather that there may be ‘opportune windows’ within the respiratory cycle that are more or less conducive to focus or mind wandering. It appears though the OAs are taking greater advantage of these opportune windows for both task engagement and disengagement, whereas the YAs are more biased towards being alert during the entrainment window. This is consistent with evidence from the YAs’ lesser SSVEP slope and more variable pre-target alpha, indicating that the YAs tune into the task only when required by the target. The significant increase in PD over the entrainment window exhibited by the OAs non-entrainers may indicate that this pattern is a natural respiratory-PD fluctuation, at least in this context, that is accentuated by significant entrainment.

Turning to the EEG frequency power spectrum, for both groups, frontal delta and theta, and posterior alpha were significantly lower over exhalation and higher over inhalation, peaking at early-to-mid inhalation. The OAs demonstrated stronger modulation of delta, theta, and alpha over the respiratory cycle. A recent review on the electrophysiology of mind wandering concluded that mind wandering episodes and internally oriented attention more generally were characterised by increased frontal delta and theta, and posterior alpha (Kam et al., 2022). Thus, the changes seen in delta, theta and alpha is also consistent with the interpretation of the PD analysis of early-to-mid inhalation facilitating a mind wandering type 'attentional break'. The stronger modulation of these slower frequencies by the OAs is also consistent with the idea that by applying their arousal/attentional system strongly to the task, there is a stabilisation between respiration and central nervous system oscillations. It appears that both the OAs entrainers and non-entrainers show a broadly similar pattern with regards to their delta, theta, and alpha power, which would indicate that this is a natural fluctuation irrespective of entrainment. However, there does appear to be a slightly delayed onset of inhalation-related power increases in the entrainers compared to non-entrainers, and secondly, the pattern for the YAs is fairly diminished amongst the non-entrainers for delta and theta and is starkly different for alpha, which implies entrainment has had an effect. Drawing a similar interpretation to the PD analysis, it's possible that respiratory-task entrainment influences an intrinsic phase-amplitude relationship with these brain oscillations. The result of entrainment here appears to be a wider window in which frequency power is intermediate which aligns with the entrainment period.

The pattern for the SSVEP is more difficult to interpret. For the YAs, it is an intriguing finding that their SSVEP is more significantly modulated over the respiratory cycle than any other variable, being particularly low in the first half of inhalation and particularly high outside of this time. This pattern indicates a window for a different sort of attentional break over early to mid inhalation. Significantly lower SSVEP signal over this period suggests a an inhibition or disengagement from sensory signals, and is consistent with the rises in the other frequencies, associated with internally oriented attention (Kam et al., 2022). It’s possible that the strong application of visual attention to the task stimulus by the OAs overrides this effect, however this interpretation is confused by the fact that the OAs entrainers mimic this pattern to a greater extent than the OAs non-entrainers whilst the YAs entrainers and YAs non-entrainers exhibit similar patterns. What is also interesting is that the dip in SSVEP for the entrainers is more tightly coupled to inhalation onset than the rise in other frequencies. Perhaps this is a naturally occurring cyclic modulation of visual processing in this task which is enhanced by entrainment, and the inhale-related dip represents the first step of attentional disengagement. There is good evidence that perceptual decoupling occurs during mind wandering (Schooler et al., 2011) to reduce interference with internal mentation. It is possible that this process is being modulated by respiration here.

We now turn to the modulation of RTm and Focus reports over the respiratory cycle. Significant modulation of RTm over the respiratory cycle has been previously observed across a range of paradigms (Johannknecht & Kayser, 2022), and we support these findings in our own task. However, this is the first study to show such an effect for subjective experience, i.e., reported Focus. As with the other measures, these effects were largely seen in the OAs group and thus adds further support to the idea that the exploitative focus applied by the OAs enhances stability between respiration and other oscillations, these ones being cognitive and experiential. Enhanced task performance or perceptual sensitivity has been observed during both inhalation (Kluger et al., 2021; Perl et al., 2019; Zelano et al., 2016), and exhalation (Buchsbaum & Callaway, 1965; Flexman et al., 1974; Grund et al., 2022), and thus respiratory phase-specific ‘advantages’ are likely to be task- and measure-dependent. Additionally, the RTm effect we observed was largely driven by the entrainers and thus this may play a key contributing role. In our task, the early inhalation phases were associated with quick RTs which roughly lines up with the latter portion of the entrainment window, as well as higher Focus reported by the OAs. Coherent with the previous interpretations, there is a significant decrease in Focus over mid-inhalation, where we propose there is an opportune window for task disengagement. The YAs Focus modulation was driven by the entrainers who interestingly showed an additional period of higher Focus in early exhalation. The OAs Focus pattern was consistent across entrainers vs non, therefore, experiencing such a modulation may depend on both entrainment and applied focus.

From what we have outlined above, we conclude that there are intrinsic, although probably context-specific, respiratory modulatory patterns of behavioural, experiential, and physiological oscillations which can be stabilised by the degree of top-down attention applied to a task, leading to more defined and temporally predictable periods of fluctuations. Respiratory entrainment also appears more likely to occur when attention is more strongly applied and may take advantage of such fluctuations to align target expectancy with periods of intermediate arousal and attention, but also utilise periods conducive to attentional disengagement from the task.

This conclusion is consistent with the perspective of an intrinsic respiration-attention coupling which can vary according to frontal and respiratory inputs to the LC (Melnychuk et al., 2018), which we discussed briefly in conjunction with the PD findings. Previous research by this group has shown significant coupling and Granger causality between respiration, PD, and frontal EEG during quiet rest (Melnychuk et al., 2021). Our present work provides additional evidence for this model by showing that PD and frontal EEG are modulated by the respiratory cycle during a sustained attention task, further implicating the LC, frontal attentional networks in a coupled relationship with respiration. Importantly, the strength of coupling, i.e., the significance of modulation, appears dependent on the strength of top-down applied attention to a task and the degree of entrainment between respiration and the task. These may be fruitful parameters to experiment with in the future to better understand how respiration and attention are interacting with each other. This is also consistent with the finding from Melnychuk et al. (2018) who showed that participants with relatively lower reaction time variability, indicative of more stable attention, were more likely to entrain their respiration to responses in an auditory oddball task.

We also believe our work is consistent with the predictive coding framework of respiration and cognition through the action of respiratory brain modulation oscillations (RMBOS). In a recent paper from Brændholt et al., (2023), they suggest three key paths of influence, with respiration interacting through (i) phase-phase (1:1) coupling with orbitofrontal oscillations providing respiratory rhythm information, (ii) phase-amplitude coupling with faster cortical oscillations and (iii) the ascending modulation of the LC-noradrenergic system. We did not directly test for (i) which is said to modulate the rhythm of descending prefrontal predictions, but it is interesting to consider that respiratory-task entrainment will influence this coupling. We additionally found evidence for phase-amplitude coupling (ii) in the prefrontal areas where top-down predictions are proposed to be generated (as well as posterior alpha), which were also modulated by the degree of respiratory entrainment. And we have already discussed our evidence for the LC (iii) which is proposed to “alter neural gain around the cortex, and by extension influence the precision-weighting and overall metastable dynamics of the cortical hierarchy” (Brændholt et al., 2023, pg. 6). The LC has also recently been conceptualised as signaling large prediction errors (Jordan, 2023), which could in part be informed by respiratory information. Respiratory-task entrainment should minimise prediction error in each pathway, and thus should be considered as an additional source of information to be considered within this framework as phase-phase coupling between respiration and environmental demands.

Despite our age-group difference in respiratory-task entrainment, there was still a considerable proportion of each group that did not show significant entrainment. Further research is needed to elucidate which individuals show this tendency. Respiratory-task entrainment did not significantly change over the hour of testing (Figure S2.1) and thus we lean towards it being a trait-related phenomenon rather than state. We speculate on one possibility, that it may depend on their degree of interoceptive awareness for respiration. It is unlikely that individuals are aware that they are entraining and thus is more likely a phenomenon of ‘implicit interoception’ (Murphy et al., 2016). However, it would be intriguing to test individuals on their explicit respiratory interoception (e.g. Patsenko et al., 2019) and note associations with entrainment across different paradigms. Efforts encouraging respiratory awareness have been seen to improve attention and reduce mind wandering in proceeding tasks (Mrazek et al., 2012; Patsenko et al., 2019). Heartbeat interoceptive sensitivity has also been seen to facilitate aspects of cognition for older adults (Murphy et al., 2018). It has also been seen that heartbeat interoceptive accuracy declines with age (Haustein et al., 2023), which would possibly be at odds with an interpretation that our OAs have enhanced respiratory interoception. However, the link between implicit and explicit interoception, and how they might relate to entrainment is not clear, but they do provide and interesting avenue to explore.

It is curious that the age groups did not significantly differ in target presentation entrainment as well as the other task events, and in fact, the YAs group had a higher proportion of those significantly entraining to it. There was some evidence for the OAs having higher target presentation entrainment as seen by the significant main effect of group when testing for change over blocks, but just not when collapsing across all blocks in the main analysis. The lack of difference here is also inconsistent with the significant difference in thought probe (TP) presentation which should be occurring with the same temporal expectancy the target. Although, these events are not directly comparable as there were 3 times as many targets as TPs and perhaps the latter was swayed by a few highly entraining participants. However, it is also worth noting that target and TP presentations occurred with variable intervals of 3, 5, and 7 s, which highlights the impressive high adaptability of respiration to entrain to varying rhythms, as well as a possible source of variation. It would be intriguing to experimentally manipulate inter-trial intervals to note what is conducive for respiratory-task entrainment. It is also possible that respiratory entrainment is more tightly coupled to motor responses, since the age-group difference in target response and particularly TP response was much higher. The TP response was also the action that re-commenced the task, which is a similar effect to Perl et al. (2019) demonstrating that trials were also preferentially initiated by participants in early inhalation. Interestingly, another study showed that volitional, spontaneous motor action was associated with exhalation (Park et al., 2020), which indicates that the consequence of motor actions can affect respiratory entrainment phase.

In conclusion, our study highlights an intricate interplay between respiratory and attentional dynamics and how this coupling may be shifted according to top-down attentional control and respiratory entrainment to a task. We believe that both factors work in conjunction through action of the LC as well as RMBOs in cortical areas to stabilise physiological and experiential fluctuations in attention. We have highlighted the specific patterns in these respiratory phase-modulated indices which should encourage future research into cyclic fluctuations in cognition broadly. This is the first study to show a group difference in respiratory-task entrainment; however, much more work is needed to elucidate inter-individual differences. It is also the first study to show respiratory modulation of subjective state, and this could have wide ranging implications for accounting for behavioural variability generally.

Appendix 2.1 – Age group differences in behavioural, experiential, and physiological signatures of attention

Behaviour and Experience Sampling

In response to TPs, OAs on average indicated 'Focused' 13.27 ± 0.65 / 16 times, versus reporting 'mind wandering', compared to YAs who indicated 'Focused', which was significantly higher: $t(70) = 4.83$, $p < 0.001$, $d = 1.14$. Otherwise, task performance-related behavioural variables were not significantly different between the groups (Table S2.1). These findings echoed Moran's (2021), except for their additional finding of OAs having significantly lower RT CoV.

Target-Locked Neural Indices

Target-locked neural indices are plotted in Figure S2.1. Testing for differences between the age groups in parameters of the indices, the OAs showed: a significantly more negative post-target SSVEP slope, $M = -0.003 \pm 0.0006$, than YAs, $M = -0.0003 \pm 0.0007$, $t(60) = -2.48$, $p = 0.016$, $d = 0.27$; a significantly lower near-response LHB slope, OAs $M = -0.002 \pm -0.0008$, YAs $M = -0.001 \pm 0.0008$, $t(60) = -2.86$, $p = 0.006$, $d = -0.73$; and a significantly lower pre-target alpha power CoV, OAs $M = 0.24 \pm 0.01$, YAs $M = 0.29 \pm 0.02$, $U = 327$, $p = 0.03$, $r = -0.32$ (Table S2.2). These findings echoed Moran's (2021).

Behaviour and Experience Sampling

Independent Samples T-Test

	t	df	*p*	Cohen's *d*
RTm	1.227	70	0.224	0.290
RT CoV	-1.096	70	0.277	-0.259
HR	-0.465	70	0.644	-0.110
FA	1.377	70	0.173	0.325
Focus (MW)	(-)4.826	70	**< 0.001**	1.139

Table S2.1 – Results from means comparison tests between the age groups, OAs and YAs, testing for differences in task performance and experience sampling focus. The two groups did not significantly differ ($p > 0.05$) with regards to task performance metrics, but the OAs did report significantly higher ($p < 0.001$) 'Focus' rather than 'Mind Wandering' (MW), in response to thought probes (TPs). FA = False Alarms.

Target-Locked Neural Indices Parameters

Independent Samples T-Test

	t	**df**	***p***	**Cohen's *d***
CPP Peak Amp	-1.535	60	0.130	-0.391
CPP Peak Latency, ms	0.396	60	0.693	0.101
CPP Slope	-0.787	60	0.434	-0.200
SSVEP Mean Amp^a	-1.593	50.2	0.117	-0.398
SSVEP Slope	-2.476	60	**0.016**	-0.630
LHB Mean Amp	-1.444	60	0.154	-0.368
LHB Slope	-0.833	60	0.408	-0.212
LHB Trough	-1.679	60	0.098	-0.427
LHB Slope (Response)	-2.861	60	**0.006**	-0.728

Mann Whitney-U Test

	U	***p***	**Rank-Biserial Correlation**
Alpha CoV	327	**0.032**	-0.317

Table S2.2 - Results from means comparison tests between the age groups, OAs and YAs, testing for differences in parameters of target-locked neural indices. OAs showed a significantly lower post-target SSVEP slope, lower pre-target alpha CoV, and lower near-response LHB slope ($p < 0.05$).

[a] *Welch’s T-Test*

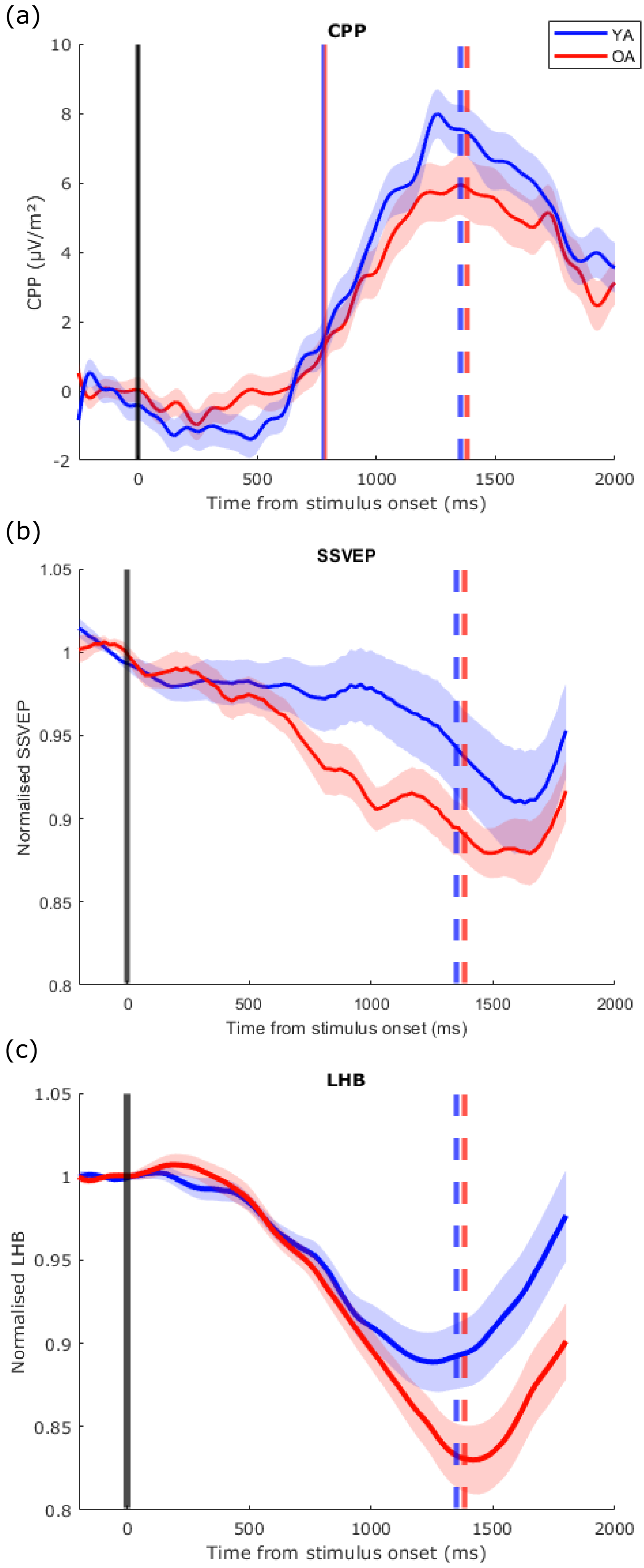


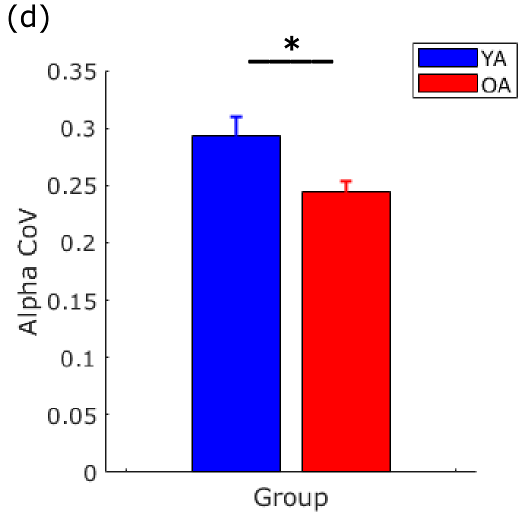
Figure S2.1 - Grand average target-locked neural indices (a), (b), and (c) OAs shown in red, YAs in blue, lighter shading shows standard error of the mean (SEM); solid black vertical line represents time of target presentation; dashed red and blue vertical lines represent respective group mean reaction time (RTm).

(a) - CPP derived from electrode A4 - indicates decision formation. Solid red and blue lines show the onset latency of the positivity which was highly similar between groups. The peak and slope were also similar.

(b) - SSVEP derived from electrode A22 from OAs and A30 from YAs - indicates sensory encoding of the stimulus fading in contrast. The slope (350 - 850 ms) was significantly more negative for the OAs vs YAs (p = 0.016).

(c) - LHB derived from electrode D19 - indicates motor preparation. The OAs showed a significantly more negative slope in the 300 ms proceeding the RTm (p = 0.006).

(d) - Between-trial, pre-target alpha CoV derived from electrodes A9, A10, B7, and B8 for both groups - indicates variability in attention. Error bars indicate SEM. Alpha CoV was significantly higher in YAs (p = 0.032), indicated on graph with ‘*’.



Pupil Diameter

With regards to post-target, target-evoked PD measures, OAs had a significantly higher mean amplitude, $M = 0.06 \pm 0.02$, YAs $M = -0.01 \pm 0.02$, $t(65) = 2.52$, $p = 0.01$, $d = 0.62$, and a higher peak amplitude, OAs $M = 0.39 \pm 0.04$, YAs $M = 0.20 \pm 0.03$, $t(65) = 3.63$, $p < 0.001$, $d = 0.90$ (Table S2.3). These findings are consistent with Moran's (2021), however they also found that OAs had a significantly lower, and more positively sloped pre-target PD than YAs, which was absent in our analysis. Instead, our pre-target PD plots showed high variation (Figure S2.2).

Target-Locked Pupil Diameter (PD) Indices

Independent Samples T-Test

	t	**df**	***p***	**Cohen's *d***
Pre-Target PD Mean Amp	-1.164	65	0.295	-0.260
Pre-Target PD Slope	0.908	65	0.325	0.245
Post-Target PD Mean Amp	2.529	65	**0.014**	0.624
Post-Target PD Peak Amp	3.536	65	**<0.001**	0.895

Table S2.3 – Results from means comparison tests between the age groups, OAs and YAs, testing for differences in target-locked PD amplitude (amp) and slope. The OAs showed a significantly greater post-target PD mean amp (p < 0.05) and peak amp (p < 0.001).

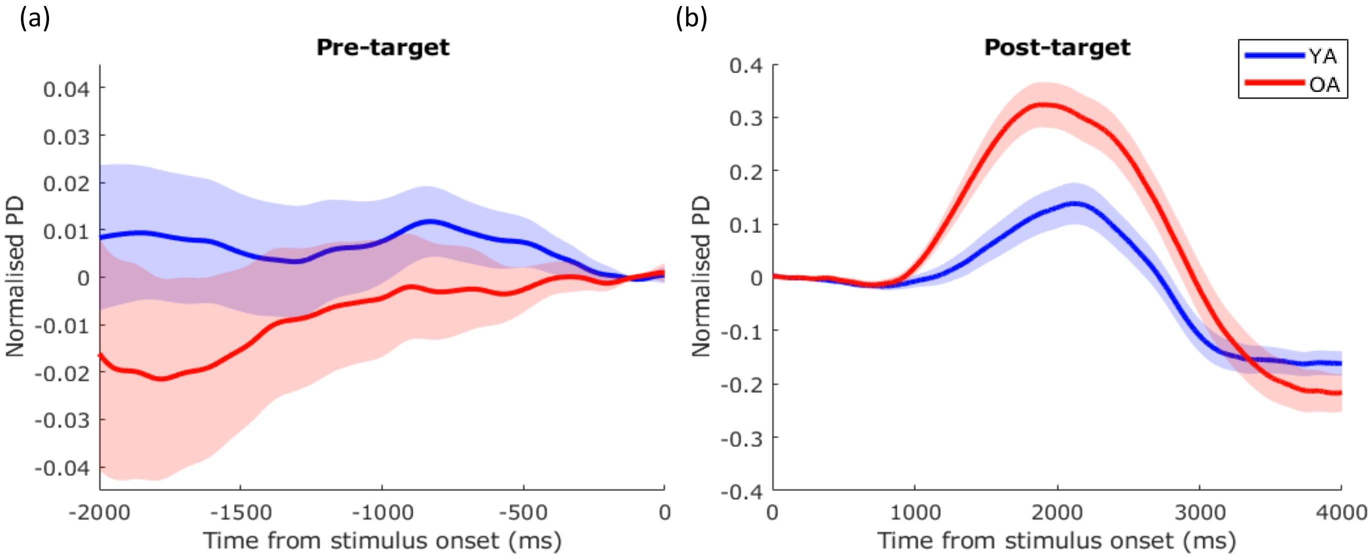


Figure S2.2 - Grand-averaged, normalised, target-locked pupil diameter (PD) for both groups, OAs (red), and YAs (blue). Shaded area indicates standard error of the mean (SEM). (a) Pre-target PD appeared to show relatively high variability, with no significant differences between the amplitude or slope. (b) Post-target PD showed an evoked response peaking at around 2000 ms. The OAs had a significantly higher mean (p = 0.014) and peak (p < 0.001) amplitude.

Trial numbers contributing to physiological indices analyses

Index	**OAs *M***	**YAs *M***
CPP, SSVEP, LHB	199 ± 17	193 ± 17
Pre-target PD	259 ± 4	332 ± 1
Post-target PD	260 ± 4	330 ± 2

Table S2.4 – Mean number of valid trials that each participant had to contribute to the respective target-locked physiological index. Values are given as means (*M*) ± the standard error of the mean (SEM). There were 384 targets over the total task, and we deemed these means to provide contribute meaningful participant averages for each index.

Appendix 2.2 – Additional supplementary analyses

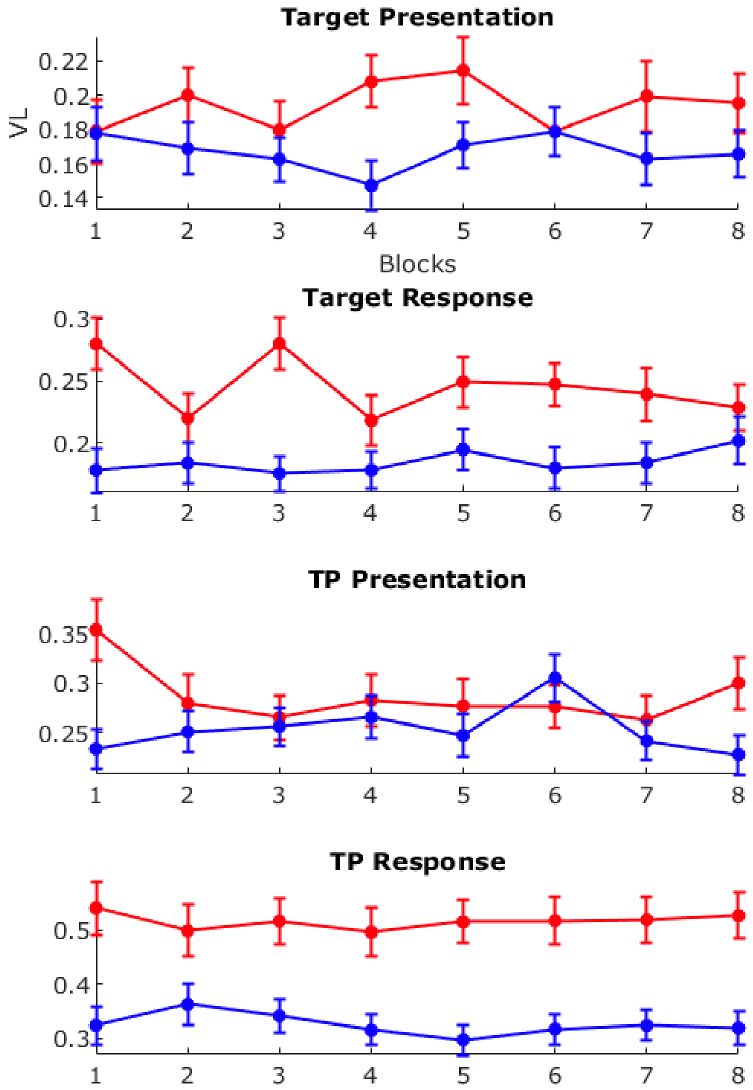


Figure S2.3 - Respiratory-task event entrainment vector lengths (VL) across blocks, split by age groups - YAs (blue), OAs (red). Error bars indicate standard error of the mean. There was no significant main effect of block for any task event, or significant interaction effect, just significant main effects of group: target presentation p = 0.03, target response p < 0.001, TP presentation p = 0.02, TP response p < 0.001.

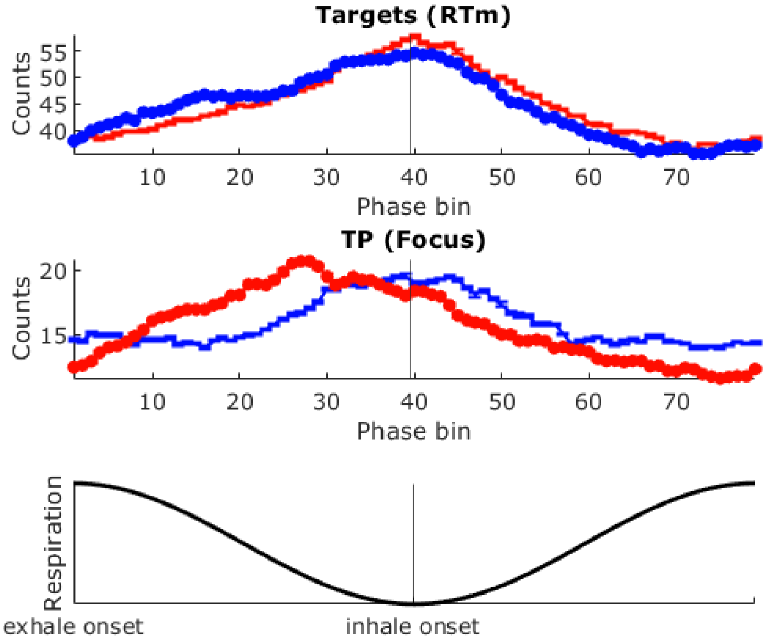


Figure S2.4 - Scatter plot of the mean number of instances of targets and thought probes within each phase bin to calculate the reaction time mean (RTm) and Focus, respectively, for the analysis exhibited in Figure 6. YAs in blue, OAs in red, error bars indicate standard error of the mean. Respiratory waveform shown on the bottom plot for reference.

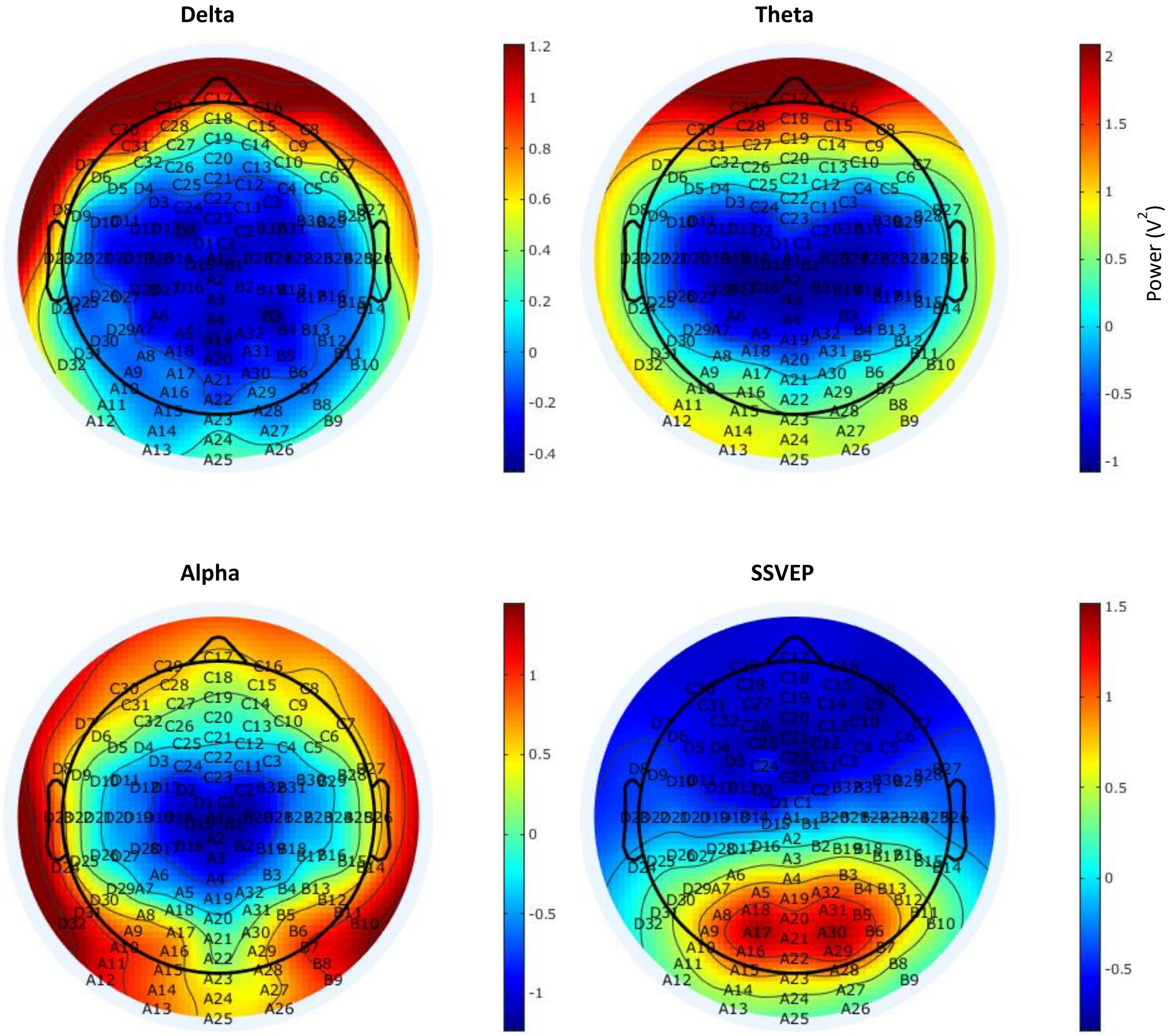


Figure S2.5 - Topographic plots of grand averaged power for frequency bands across the whole task. For the analysis in Figure 8, these plots informed of electrodes exhibiting maximal power. For delta (1 - 4 Hz) and theta (4 - 7 Hz), electrodes C16, C17 and C29 were selected. For alpha (8 - 14 Hz), A11, B10 and D32, and for the SSVEP (25 Hz), A17 and A30.

Empirical Chapter 3

Introduction

The spontaneous respiratory rhythm is intermixed with breaths which are larger in volume of the average breath. These breaths are referred to in the literature as ‘sighs’, and are believed to have a fundamental role in maintaining healthy respiratory dynamics (Vlemincx, Van Diest, et al., 2010).

Spontaneous respiration is not constant in terms of rate and volume, but rather it contains considerable variability which is thought to facilitate flexibility in the system, allowing it to adapt to changing states (Vlemincx, Van Diest, et al., 2010). For example, respiration adapts to different arousal (Balban et al., 2023; Shea, 1996; Yackle et al., 2017) and emotional states (Boiten et al., 1994; Jerath & Beveridge, 2020), and more recently, it is becoming increasingly recognised that respiration entrains its rhythm to sensory-cognitive demands in a wide-ranging manner (Grund et al., 2022; Huijbers et al., 2014; Johannknecht & Kayser, 2022; Melnychuk et al., 2018; Perl et al., 2019; Zelano et al., 2016).

A large body of work has been done by Vlemincx et al., to demonstrate that sighs can be viewed as a component within a dynamic respiratory system which acts as both a physiological (Severs et al., 2022) and psychological (Vlemincx et al., 2022) resetter. Physiologically, sighs reset variability in respiratory rate or volume, they counteract atelectasis (alveoli collapse), and have links to transitioning between arousal states. Psychologically, sighs appear to occur during stressful scenarios and induce feelings of relief.

A large focus has been on the corrective action that sighs take to reset respiratory variability. Optimal respiratory variability is that which can carry out the fundamental gas exchange function, but also maintain adaptability to changing states. The research group have shown that a ‘non-stressful’ sustained attention task was associated with participants having low respiratory variability and an increased sigh frequency in the subsequent recovery period. When participants performed a ‘stressful’ mental arithmetic task, their respiratory variability was high and sigh frequency also increased compared to rest (Vlemincx et al., 2011, 2012a). They also showed here that both spontaneous and instructed sighs after the tasks had an effect of resetting the variability (Vlemincx et al., 2012a). The authors partial out “correlated variability” and “random variability”, with the former represented by the degree of autocorrelation in respiration at one breath lag, and the latter inferred by the remaining variability in the total variability (coefficient of variation), that is not correlated. They have also demonstrated that sighs reset increases in random variability over a period of quiet rest (Vlemincx, Van Diest, et al., 2010).

As well as resetting respiratory variability, it is thought that sighs have a role in facilitating shifts between arousal states (Ramirez, 2014; Severs et al., 2022). The evidence for this is largely through observing sighs around arousal behaviours during sleep (Perez-Padilla et al., 1983; Ramirez et al., 2013), as well as possible linkages to the locus coeruleus noradrenaline system (Severs et al., 2022; Viemari et al., 2013). Akin to the resetting of variability, sighs may also reset arousal as it has been seen that sighing increased in response to high-arousal negatively valanced images (Vlemincx et al., 2015). Relatedly, the psychological counterpart to these physiological resets appears to be the experience of relief (Vlemincx et al., 2009, 2016; Vlemincx, Taelman, et al., 2010).

Within the present thesis, we have investigated a relationship between respiration and attention from the perspective that they are coupled oscillators (Melnychuk et al., 2018, 2021). If such an inherent linkage exists, the fundamental role that sighs appear to have in maintaining optimal respiratory variability should also implicate sighs in altering attentional states. The association between sighs and arousal already provides preliminary evidence given the close association between arousal and attentional systems (Aston-Jones & Cohen, 2005b). The prior two empirical chapters within the present thesis were analyses of two datasets with two different sustained attention tasks. In light of the prior work discussed, showing that respiratory variability and sigh behaviour is altered by attentional tasks of low and high demand (Vlemincx et al., 2011, 2012a), we saw opportunities to attempt to corroborate these previous findings and then extend them from the perspective of a respiratory-attentional coupling.

In Empirical Chapter 2 (EC2) we reported that participants entrained the rhythm of their respiration to the events in the sustained attention task, e.g., target presentation. This task (Gradual Contrast Change Detection – Experience Sampling) was monotonous and of low demand and thus we could expect to see a reduction in respiratory variability and frequent sigh behaviour based on earlier findings by Vlemincx et al. However, participants entrained their respiratory rhythm to task events of variable inter-presentation intervals, and thus, this should have instead induced considerable random variability into their respiration. Sighs may therefore increase in frequency here, to reset variability, to maintain adaptability, and facilitate further entrainment. Either way, we should expect to see frequent sigh behaviour and we intend to investigate here whether a sigh resets the respiratory variability, corroborating previous findings.

From the perspective of a respiratory-attentional coupling, and association between sighs, arousal, and relief, we further hypothesise that participants' task attention could be 'reset'. We intend to test this by comparing thought probe responses and reaction times either side of sighs for an indication of subjective and objective task focus respectively. To our knowledge, no prior studies have tested for a pre- to post-sigh difference in task performance or experiential focus.

In Empirical Chapter 1 (EC1) we reported that a slow-paced breathing intervention was related to participants committing less task errors than a control group who were breathing naturally in the Paced Auditory Cue Entrainment (PACE) task. Firstly, we are curious to investigate whether the breathing intervention had any influence on sigh frequency. Vlemincx et al., (2012b) asked participants to perform various breathing patterns and noted that all of them increased sigh frequency. However, sigh frequency was primarily predicted by the increased effort and tension that these imposed breathing patterns induced, compared to spontaneous breathing (Vlemincx et al., 2012b). They did not include a slow-paced breathing pattern and instead included a rigid pattern that controlled respiratory volume, and additionally, qualitative assessments of our participants did not indicate discomfort or difficulty following the breath guide. Thus, our data may not be directly comparable, however we could predict from prior theorising that there should be an increase in sigh frequency due to the induced low variability of paced breathing. We also have behavioural responses within this dataset which can be tested pre- to post-sigh as discussed above.

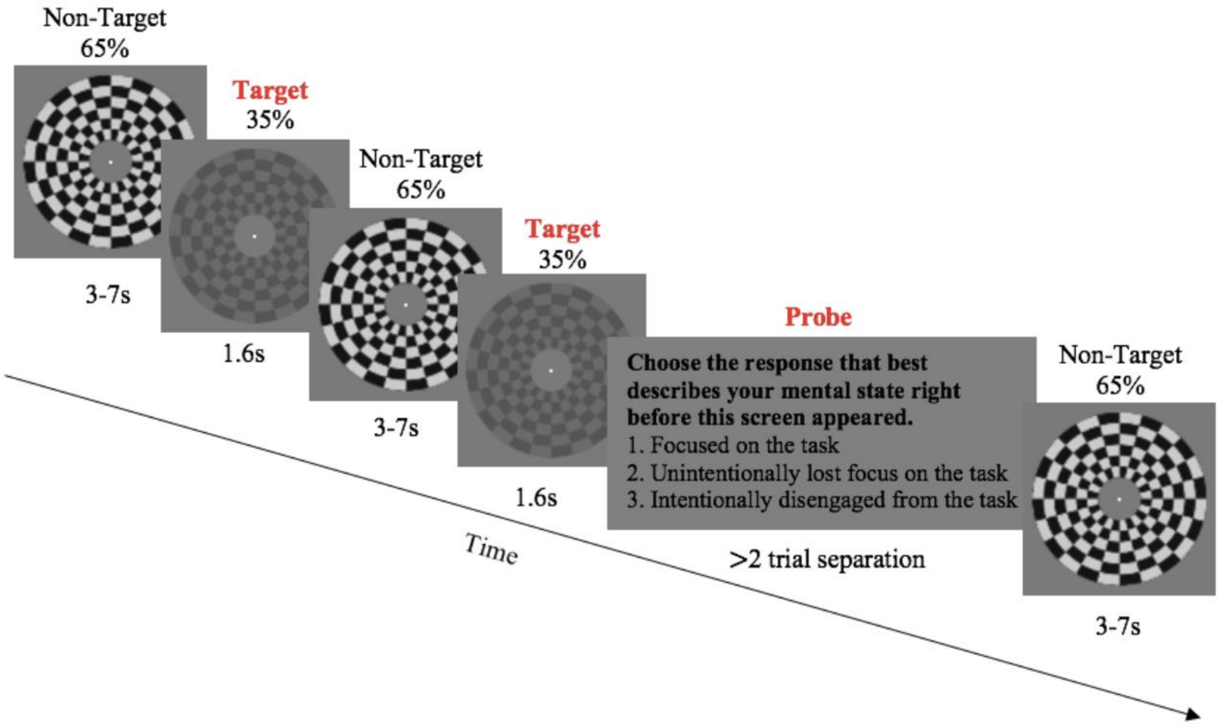
Another central theme of the present thesis is the possibility that respiration and attention are coupled via the locus coeruleus – noradrenaline (LC-NA) system (Melnychuk et al., 2018, 2021). It has been seen in mice that activation of beta-noradrenergic receptors in the preBötzinger complex specifically induce sigh behaviour, leaving spontaneous respiration uninfluenced (Viemari et al., 2013). It has not yet been tested whether changes in noradrenergic activity relate to sigh behaviour in humans. In humans, LC-NA activity can be accessed using pupil diameter (PD) as a proxy measurement (Bang et al., 2023; DiNuzzo et al., 2019; Elman et al., 2017; Meissner et al., 2023; P. R. Murphy et al., 2014), and we have continuous PD tracking in our datasets. We predict that our monotonous, demand tasks will have induced low arousal states in participants and thus sighs may act to increase arousal which should be concomitant with an increase in PD. This would also be consistent with the finding that respiratory depth closely follows PD (Kluger et al., 2023; Ohtsuka et al., 1988), and a sigh has a larger than normal volume.

Methods

Analysis for the present study on sigh behaviour was performed on data acquired for two separate larger analyses within this thesis, in EC1 and EC2.

In EC1, participants performed the Paced Auditory Cue Entrainment (PACE) task (Figure 3.1b). The ‘Instructed Breathing’ (IB) group for this study were instructed to respond to auditory tone stimuli with rhythmic mouse clicks, and additionally, use the tone stimuli as a slow-paced breathing (0.1 Hz – 0.15 Hz) guide. The ‘No Instructed Breath’ (NIB) group was told only to respond to the tones with mouse clicks. Analysis for the present study was performed on these groups separately due to the breath manipulation and it is clearly stated whether the analysis pertains to the IB or NIB group.

In EC2, participants comprised of younger adult (18-35 y/o; n = 38) and older adult (65-80 y/o; n = 34) groups, who performed 8 blocks of a sustained attention task – the Gradual Contrast Change Detection – Experience Sampling Task (Figure 3.1a). Participants had to respond with a mouse click when the onscreen stimulus diminished in contrast, as well as responding to thought probes which assessed their subjective task focus vs mind wandering. For the purposes of the present analysis, age groups were collapsed, and analyses were performed on the whole sample. This was justified since when performing each analysis separately on each group, the statistical conclusions were the same, and thus we took advantage of the increased power from a greater sample size. This dataset will be referred to as dataset Grad.



Choose the response that best describes your mental state right before this screen appeared.

1. Focused on the task
2. Unintentionally lost focus on the task
3. Intentionally disengaged from the task

Figure 3.1a - Schematic of the Gradual Contrast Change Detection with Experience Sampling (GradCCD-ES) Task. A continuously presented checkerboard, anulus stimulus decreases in contrast after variable intervals which is the target to be identified by participants, who respond with a mouse click upon recognition. Additionally, the stimulus is interrupted with experience-sampling thought probes (TPs) which ask the participant to categorise their attentional state immediately prior to the TP presentation. Each block consists of 48 targets, 16 TPs and lasts approximately 8 mins each. A testing session consisted of 8 blocks.

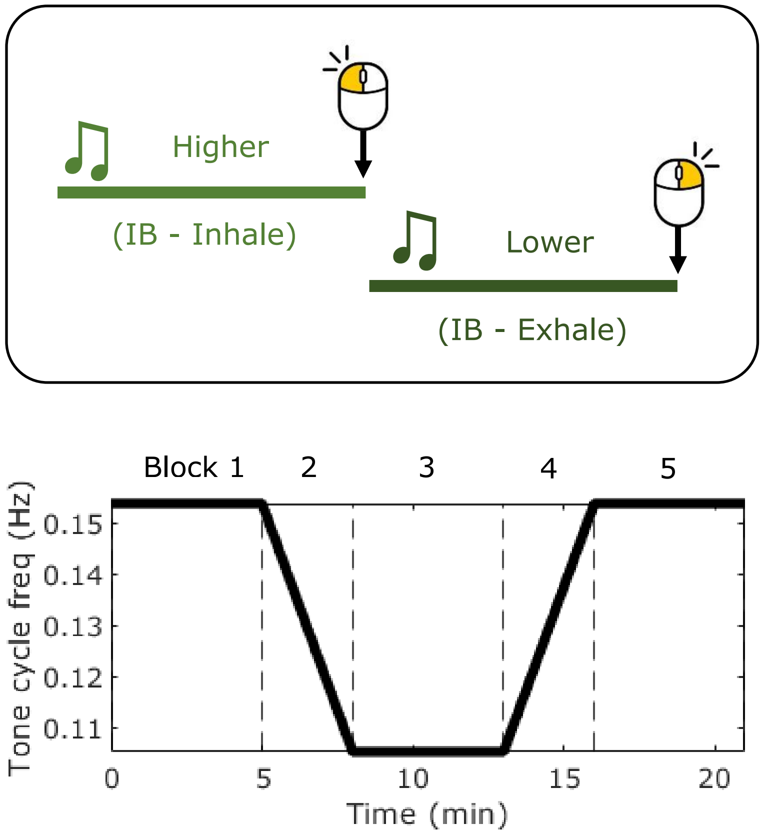


Figure 3.1b - Schematic for Paced Auditory Cue Entrainment (PACE) task. Participants heard a higher pitched tone and lower tone cycling continuously for 21 minutes. Both of which they had to rhythmically respond to with mouse clicks so that left clicks landed on the high → low transition and right on the low → high. An 'Instructed Breathing' (IB) group had to additionally inhale during the higher tone and exhale during the lower tone. A 'No Instructed Breathing' (NIB) group only responded with mouse clicks. The tone cycle frequency changed over time, starting at 0.15 Hz in block 1, slowing to 0.1 Hz in block 2, remaining at 0.1 Hz in block 3, then speeding up 0.15 Hz in block 4 and then it remained at 0.15 Hz in block 5. Thus, the rate of mouse responses and rate of respiration for IB only, changed accordingly.

Data Analysis

Recording and pre-processing methods for the respiration and pupil diameter (PD) can be found in EC1 and EC2 and was identical for each. Respiratory rate (RR) was calculated as 60 divided by the time duration between each breath to obtain a value for each breath. Inspiratory volume (Vi) was the positive peak value for each breath, and peaks were determined on participant-normalised respiratory data using MATLAB function findpeaks() with a minimum peak width of 0.5 s. The total variability of RR (RR-CV) and Vi (Vi-CV) was calculated as the coefficient of variation of the array of values for each. The correlated variability for each (RR-AR and Vi-AR) was calculated as the autocorrelation coefficient of the array of values taken at lag = 1, or one breath lag. Random variability in these measures was inferred as the remaining variability in total variability (CV). Sighs were detected as breaths that had a Vi of at least twice the mean Vi for that recording session, using findpeaks() with this minimum peak height threshold and a minimum peak width of 1 s.

In both datasets we tested for differences in respiratory dynamics means pre- and post-sigh which were derived from the 10 breaths each side of each sigh. Similarly, reaction time (RT) differences were assessed from the 3 targets prior and post each sigh. In dataset Grad we additionally assessed changes in the thought probe responses for the thought probe each side of each sigh. Thought probes were categorised into 'Focus' and 'Mind Wandering', and for each participant we obtained a Focus:Mind

Wandering ratio pre- and post- sighs based on these responses. For this analysis participants who provided less than 10 mind wandering responses were excluded.

For both datasets, PD was extracted 4000 ms either side of each sigh, baseline corrected by subtracting the prior 100 ms, and grand-averaged across sighs and participants.

In dataset Grad, EC2, we used a measure of the degree of entrainment between the participants' respiratory cycle and the presentation of targets. We refer to this as the 'target vector length' and it is a measure of variability in the respiratory phases occurring at the time of targets, where a higher vector length implies less variability (Cremers & Klugkist, 2018).

Results

It shall be clearly stated whether each analysis pertains to dataset Grad or dataset PACE. Within dataset PACE, there is also the distinction of the 'Instructed Breathing' (IB) and 'No Instructed Breathing' (NIB) groups, the former of which underwent a slow-paced breathing intervention.

Sigh frequency: In dataset Grad, there was a mean total of 79.0 ± 5.9 sighs per participant over the whole task, averaging 9.9 sighs for each of the 8 min blocks. In dataset PACE, there was a mean total of 7.0 ±

1.7 for the IB group and 16.8 ± 2.3 for the NIB group, over the 21 min task.

Sigh count correlations with respiratory variability: See Figure 3.2 for all correlation plots. In dataset Grad, sigh count was significantly positively correlated with RR-CV r(70) = 0.56, $p < 0.001$, and Vi-CV r(70) = 0.80, $p < 0.001$, significantly negatively correlated with RR-AR r(70) = -0.49, $p < 0.001$, and Vi-AR r(70) = -0.81, $p < 0.001$. Higher sigh count was related to increased inferred random variability in RR and Vi.

In dataset PACE, for group NIB, mean number of sighs was significantly positively correlated with RR-CV r(30) = 0.54, $p < 0.001$, and Vi-CV r(30) = 0.62, $p < 0.001$, significantly negatively correlated with RR-AR r(30) = -0.54, $p < 0.001$, and Vi-AR r(30) = -0.72, $p < 0.001$. Higher sigh count was related to increased inferred random variability in RR and Vi.

For group IB, mean number of sighs was not significantly correlated with RR-CV r(23) = 0.34 $p = 0.09$, or RR-AR r(23) = -0.28, $p = 0.17$. It was significantly positively correlated with Vi-CV r(23) = 0.85, $p < 0.001$, and negatively with Vi-AR r(23) = -0.87, $p < 0.001$. Higher sigh count was related to increased inferred random variability in Vi only.

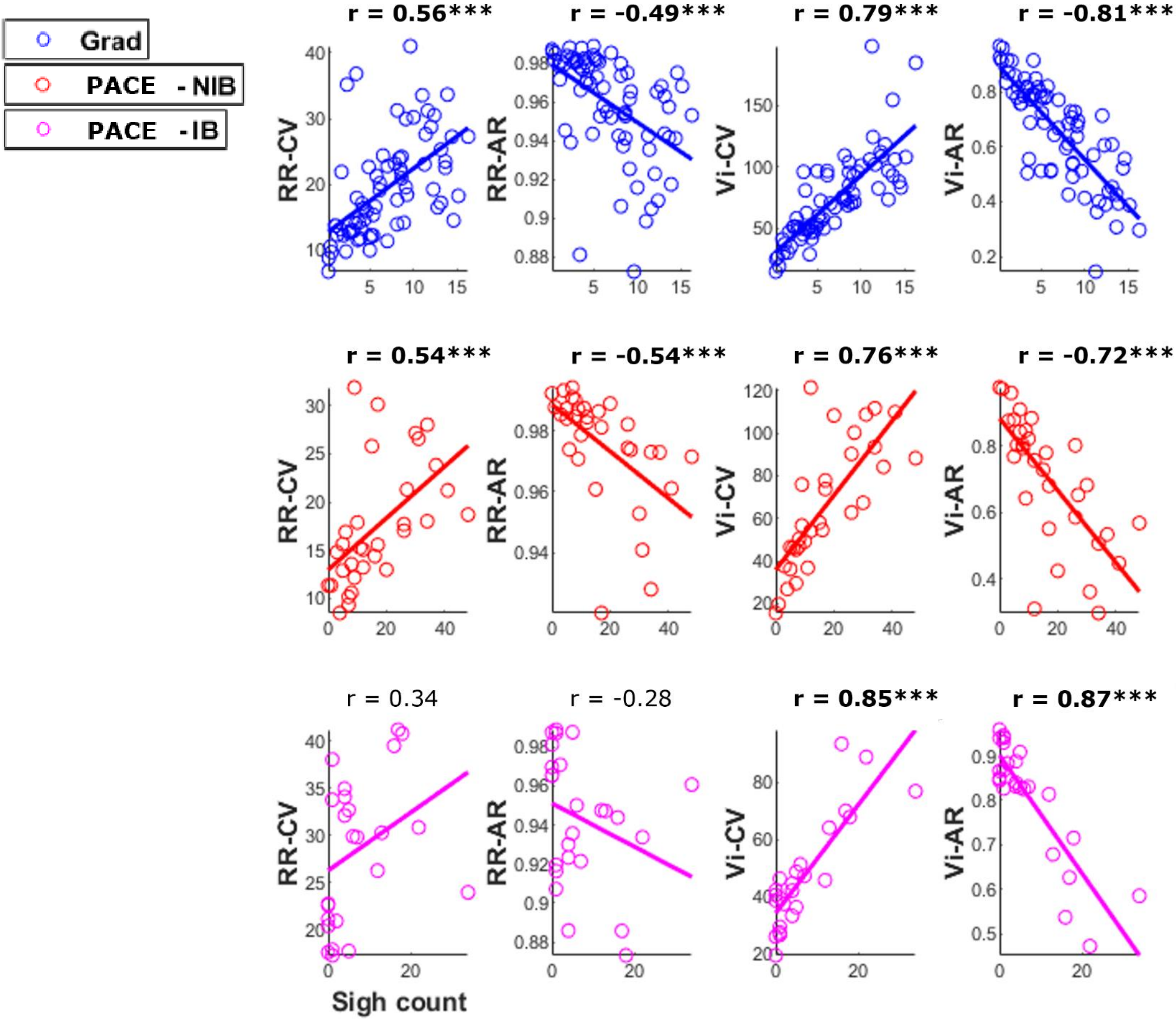


Figure 3.2 - Scatter plots between respiratory dynamics and sigh counts for dataset Grad (blue, top), and dataset PACE - NIB group (red, bottom). RR = Respiratory Rate; Vi = Inspiratory Volume; CV = Coefficient of variation, measure of total variability; AR = Autocorrelation coefficient at one breath lag, measure of correlated variability. Dots represent participant means and the line represents the line of best linear fit. Overlaid on each plot is the correlation coefficient from Pearson's correlation test between the variables. **p < 0.01, ***p < 0.001.

Sigh count and respiratory variability over blocks: See Figure 3.3 for plots. In dataset Grad, sigh count showed a fairly linear trend of increasing across the blocks, F(5.36) = 4.29, p < 0.001. All respiratory variability measures showed a significant difference over blocks, RR-CV F(5.24) = 4.82, p < 0.001, Vi-CV F(5.47) = 7.59, p < 0.001, RR-AR F(5.34) = 3.99, p < 0.001, and Vi-AR F(5.76) = 5.65, p < 0.001. RR-CV and Vi-CV showed an increase over blocks whereas RR-AR and Vi-AR showed a decrease.

In dataset PACE, an ANOVA for sigh count across blocks including both IB and NIB groups showed a significant main effect of blocks, F(2.76) = 5.58, p < 0.01, and of group, F(1) = 10.72, p < 0.01, but not interaction, F(2.76) = 2.15, p = 0.10. Post-hoc tests for block comparisons in this dataset showed a significant difference between blocks 2 and 3, p = 0.001, and blocks 2 and 5, p = 0.02. Sigh count was highest in blocks 3 and 5, and lowest in block 2 for both groups.

Respiratory dynamics were assessed separately for each group. For the NIB group, all measures significantly differed between the blocks, RR-CV F(2.92) = 3.14, p = 0.03, Vi-CV F(2.50) = 10.72, p < 0.001, RR-AR F(2.43) = 3.56, p = 0.03, Vi-AR F(3.12) = 10.80, p < 0.001, with RR-CV and Vi-CV showing an increasing trend and RR-AR and Vi-AR showing a decreasing trend. For the IB group, all measures significantly differed between the blocks, RR-CV F(4) = 19.97, p < 0.001, RR-AR F(2.18) = 13.41, p < 0.001, Vi-CV F(4) = 12.06, p < 0.001, Vi -AR F(4) = 9.36, p

< 0.001. RR-CV showed an inverted V-shaped trend, RR-AR a V-shaped trend, Vi-CV showed an increasing trend and Vi-AR showed a decreasing trend.

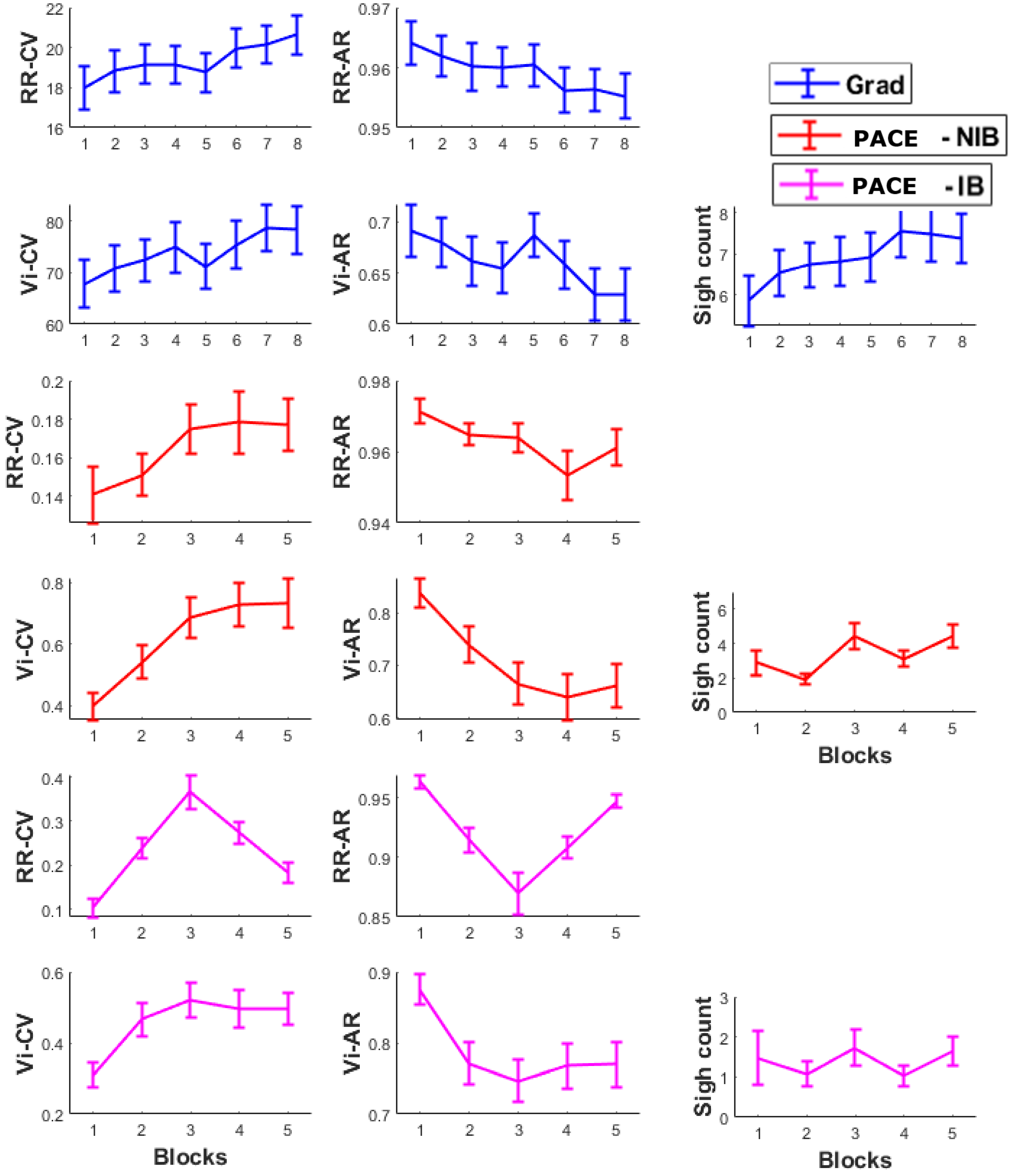


Figure 3.3 - Respiratory variability and sigh counts over blocks. Grad in blue, PACE - NIB in red, PACE - IB in magenta. RR = Respiratory Rate; Vi = Inspiratory Volume; CV = Coefficient of variation, measure of total variability; AR = Autocorrelation coefficient at one breath lag, measure of correlated variability. Error bars indicate standard error of the mean. Note different y axis scale for PACE sigh count plots.

Respiratory dynamics pre- and post-sigh: See Figure 3.4. In dataset Grad, RR-CV significantly decreased pre- to post-sigh, t(71) = 9.38, p < 0.001, and RR-AR significantly increased, t(71) = -6.93, p < 0.001, Vi-CV significantly decreased, t(71) = 5.41, p < 0.001 and Vi-AR significantly increased, t(71) = -12.08, p < 0.001.

In dataset PACE, for the NIB group, RR-CV significantly decreased, t(30) = 7.32, p < 0.001, RR-AR significantly increased, t(30) = -4.52, p < 0.001, Vi-CV significantly decreased t(30) = 2.20, p = 0.04, and Vi-AR significantly increased, t(30) = -6.97, p < 0.001. The IB group did not show any significant differences in RR-CV t(18) = 0.77, p = 0.45, RR-AR t(18) = -0.73, p = 0.48, but did show a significant decrease for Vi-CV, t(18) = 2.50, p = 0.02, and significant increase for Vi-AR t(18) = -3.98, p < 0.001.

Behaviour pre- and post- sigh: In dataset Grad, the reaction time mean, RTm t(71) = -0.83, p = 0.41, and coefficient of variation, RTCoV t(71) = 1.30, p = 0.20, from the 3 target responses either side of sighs did not significantly differ. Nor did the Focus:mind wandering ratio for the thought probe response either side of sighs, t(52) = -0.13, p = 0.90.

In dataset PACE, for the NIB group, there was no significant difference pre- to post-sigh for RTm F(28) = 0.55, p = 0.46, or RTCoV t(28) = -0.28, p = 0.78. Nor for the IB group, RTm F(17) = 0.02, p = 0.88, RTCoV t(17) = 0.06, p = 0.96.

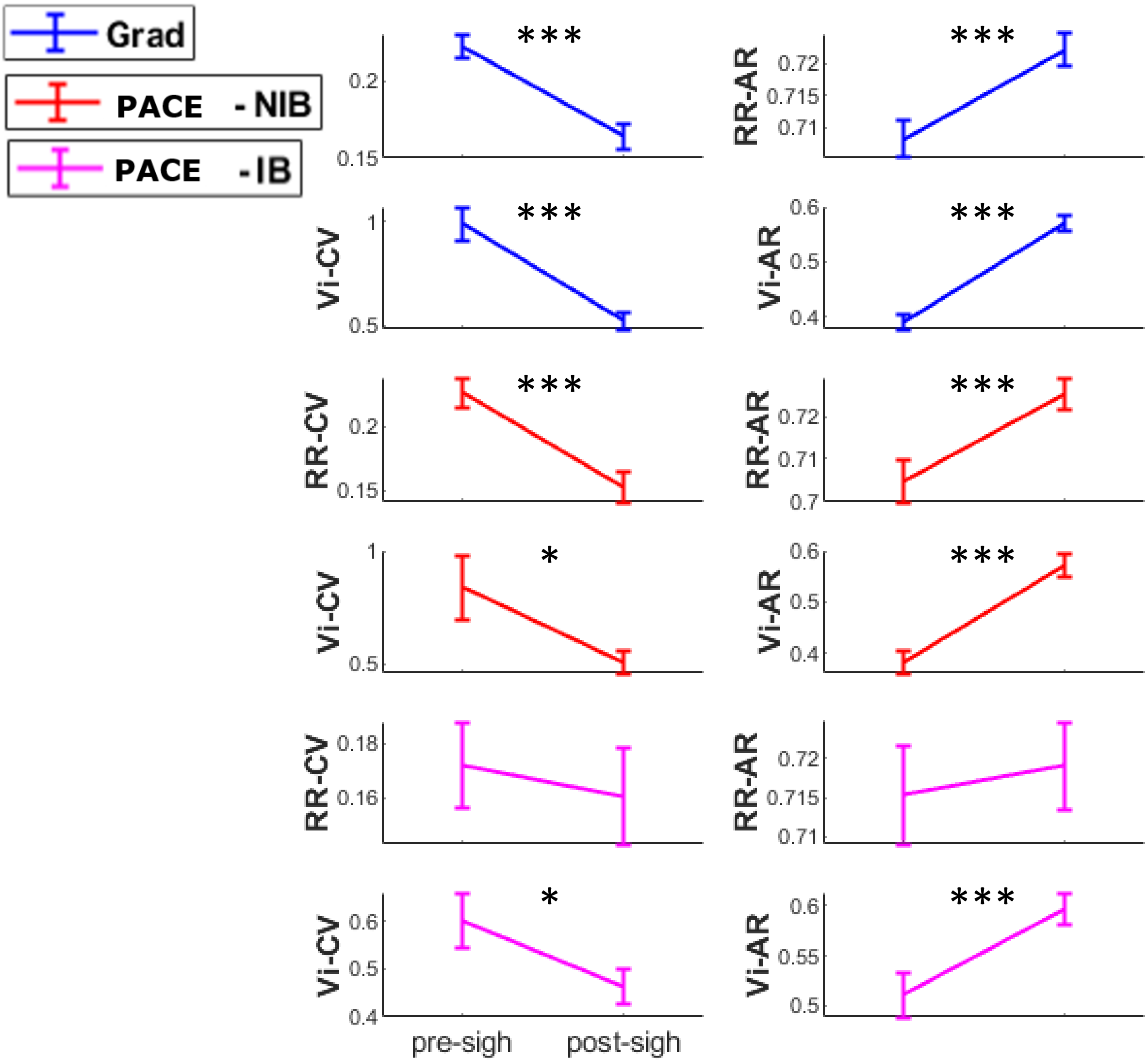


Figure 3.4 - Respiratory dynamics pre- and post-sigh. Error bars indicate standard error of the mean. Top shows dataset Grad (blue), middle is dataset PACE group NIB (red), and bottom shows group IB (magenta). RR = Respiratory Rate; Vi = Inspiratory Volume; CV = Coefficient of variation, measure of total variability; AR = Autocorrelation coefficient at one breath lag, measure of correlated variability. $*p < 0.05$, $***p < 0.001$.

Sigh count, respiratory variability, and respiratory-task entrainment: See Figure 3.5. In dataset Grad, the degree to which participants entrained their respiratory cycle to the timing of target presentation, or the target vector length, was significantly positively correlated to RR-CV $r(70) = 0.49$, $p < 0.001$, and Vi-CV $r(70) = 0.44$, $p < 0.001$, and significantly negatively correlated to RR-AR $r(70) = -0.51$, $p < 0.001$, and Vi-AR $r(70) = -0.48$, $p < 0.001$. Finally, target vector length significantly positively correlated with sigh count $r(70) = 0.34$, $p < 0.01$.

Pupil diameter over sighs: Grand averaged pupil diameters (PD) are plotted -4000 ms – to +4000 ms relative to sigh peak in Figure 3.6. In dataset Grad, PD steadily increased over the entire time course. In dataset PACE, for group NIB, PD showed an initial increase up until the beginning of inhalation, then a slight decrease before rising again beyond the respiratory peak and then steadily decreasing. For group IB, PD rose sharply in early-mid inhalation, peaking just after respiratory peak and then sharply fell.

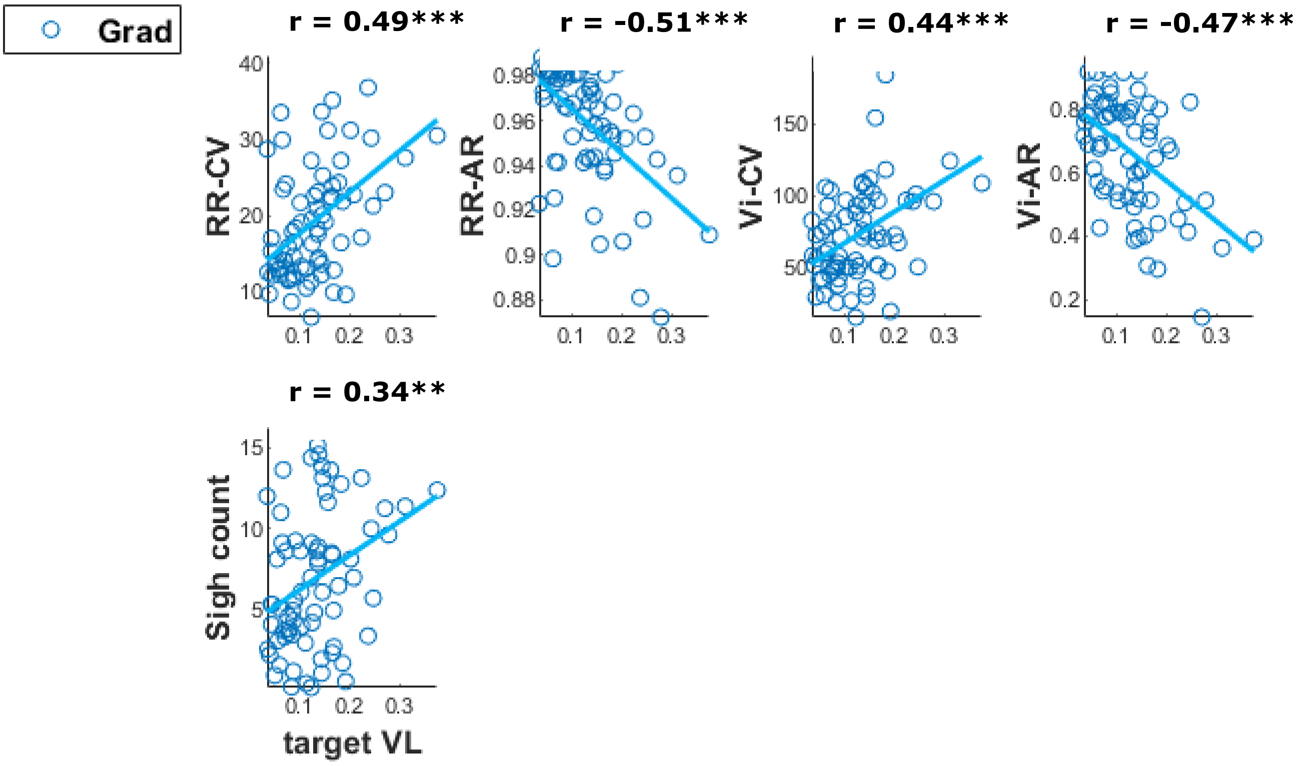


Figure 3.5 - Scatter plots between respiratory dynamics and sigh counts against target vector length (VL, entrainment measure) for dataset Grad. RR = Respiratory Rate; Vi = Inspiratory Volume; CV = Coefficient of variation, measure of total variability; AR = Autocorrelation coefficient at one breath lag, measure of correlated variability. Dots represent participant means and the line represents the line of best linear fit. Overlaid on each plot is the correlation coefficient from Pearson's correlation test between the variables. $^{**}p < 0.01$, $^{***}p < 0.001$.

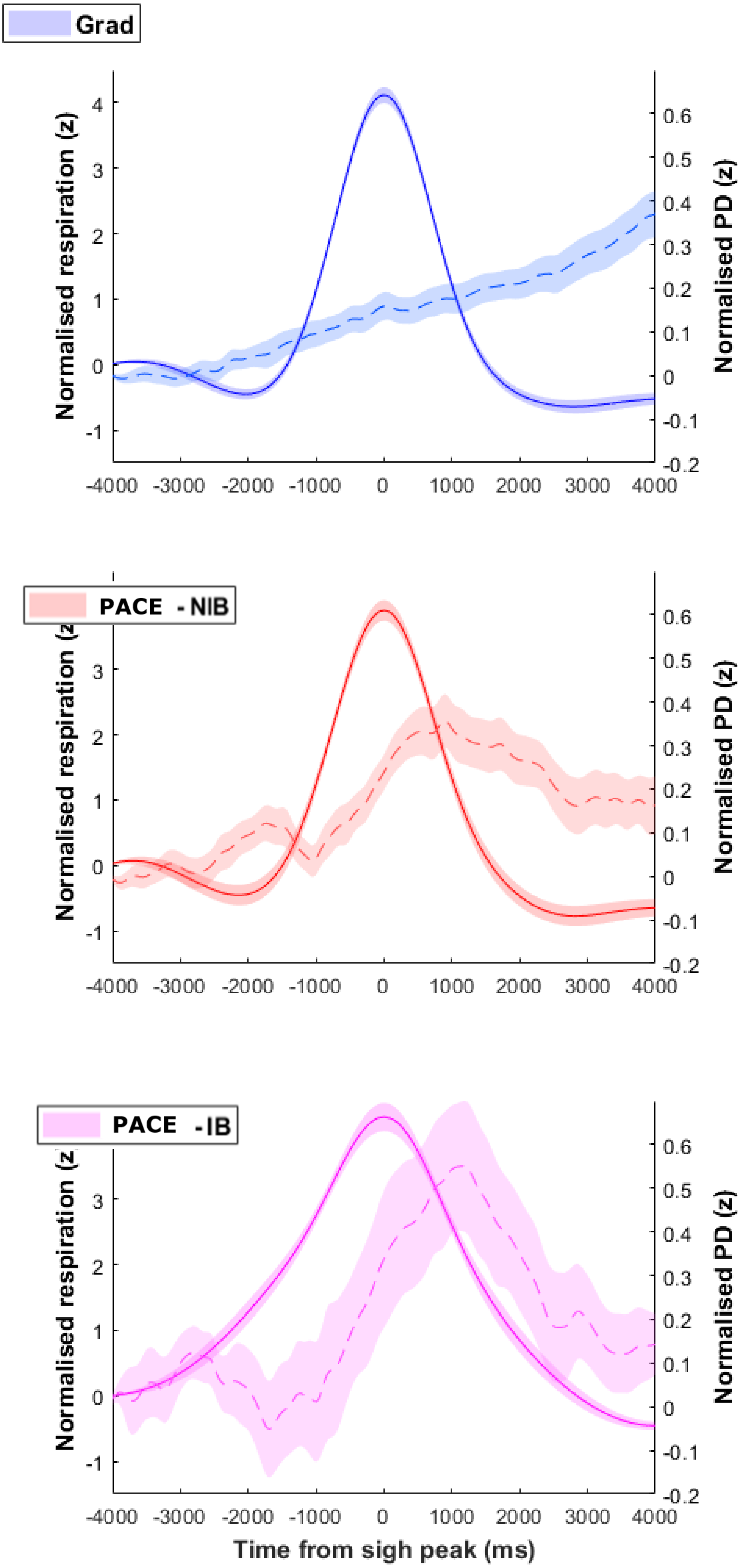


Figure 3.6 - Grand averaged respiration (solid line) and pupil diameter (PD; dashed line), -4000 ms to +4000 ms over sighs, for dataset Grad (top, blue), dataset PACE, group NIB (middle, red) and group IB (bottom, magenta). Shaded area indicates standard error of the mean.

Discussion

Across two datasets with two different sustained attention tasks, we corroborate previous findings of increased random respiratory variability during a task that is related to increased sigh frequency. Crucially, the sigh resets variability. We also discovered additional factors that correlated to sigh frequency. In dataset Grad, we previously reported significant entrainment between the participants' respiration and the timing of pseudo-randomly presented task targets. Here, we report that the degree of entrainment is positively related to sigh frequency, as well as increased random variability in respiration. In dataset PACE, the blocks where the stimuli were constant in length contained more sighs, whereas the blocks where the stimuli were changing in length contained less sighs. Both groups in this dataset showed this same pattern, despite the fact that the 'instructed breathing (IB)' group had an overall lower number of sighs than the 'no instructed breathing (NIB) group. Finally, we show for the first time in humans that sighs are related to a changes pupil diameter (PD), implicating sigh behaviour with the noradrenaline, arousal system.

Previous work has seen sigh frequency increase in the subsequent recovery period after a sustained attention task, and related to decreased variability in respiration (Vlemincx et al., 2011, 2012a). Here instead, in our sustained attention tasks, we relate sigh behaviour to increases in random variability, which is what the authors saw during a mental arithmetic task that was intended to be stressful. Although our tasks were monotonous and of very low demand, and therefore not stressful in the immediate sense, it is probable that these tedious tasks became stressful over time. Indeed, the total variability did increase over blocks, while the correlated variability decreased (only in Vi for PACE-IB).

However, whilst this trend of variability over blocks was consistent with the number of sighs in Grad, the pattern was inconsistent for PACE groups. Both PACE-IB and PACE-NIB groups had the lowest number of sighs during blocks 2 and 4, where the stimuli were changing in length each cycle. This dynamic element likely engaged participants' attention more, and there is evidence for this with the NIB group showing a lower number of errors in these blocks (see EC1, Figure 1.3b). Therefore, the level of engagement of a task period appears to influence sigh frequency.

It is also intriguing that this was also a strong driving factor in the PACE-IB group who controlled their RR. Although, despite a rigid RR pattern, their Vi showed comparable changes in variability to PACE-NIB. Previous work has shown that imposing a rigid, volume-controlled breathing pattern induced higher sighs compared to spontaneous breathing, although possibly attributable to the tension experienced as a result (Vlemincx et al., 2012b). Our finding that our paced breathing group had less sighs than our spontaneous breathing group is at odds with their finding, as well as being possibly at odds with the idea that sighs should increase from a restriction of respiratory variability. However, as aforementioned, despite controlling RR, these participants' Vi showed increases in random variability over time. Perhaps there was counteracting effects here between these two factors – it is uncertain what the relative contributions are for RR and Vi in this model. Additionally, we have already noted how higher task engagement may decrease sigh likelihood, and the PACE-IB group were likely more engaged than PACE-NIB since they had their additional breathing task to perform.

Not only were sighs correlated to random variability, analysis of variability prior and proceeding sighs shows that the sighs reset respiratory variability so that it was less variable and more correlated. This is consistent with the resetter perspective of sigh function (Vlemincx, Van Diest, et al., 2010). We hypothesised that as well as resetting respiratory variability, subjective focus and task performance could be similarly reset. We found no difference in these measures prior and proceeding sighs and there did not appear to be such an effect. In both datasets, there was very little inter- and intra-individual variability in task performance measures and so perhaps our task was not sensitive enough to pick up a difference here. Similarly, the way each participant responded to thought probes was fairly consistent across time and so perhaps any effect of a sigh would be negligible compared to their prevailing attentional state. Otherwise, it may be that sighs do not have a considerable effect on performance or attention within relatively mundane experiences. Findings that sighs produce feelings of relief were reported in studies inducing stress and high arousal (Vlemincx et al., 2009, 2016; Vlemincx, Taelman, et al., 2010).

We produce novel findings that respiratory entrainment to the Grad-CDD-ES task was related to an increased sigh frequency. Participants entrained their respiration to task events of variable inter-presentation intervals, and this appeared to induce significant random variability into their respiration. Therefore, herein lies another factor worth considering as a significant contributor to the occurrence of sighs. Respiratory entrainment to a wide range of sensory-cognitive tasks is becoming an increasingly observed phenomenon (Grund et al., 2022; Huijbers et al., 2014; Johannknecht & Kayser, 2022; Melnychuk et al., 2018; Perl et al., 2019; Zelano et al., 2016). In these studies, respiratory entrainment was also concurrent with a respiratory-phase modulation of cognition or perception, which implicates such entrainment in an adaptive function to optimise task performance. It is therefore intriguing to think that whilst this entrainment seems to provide a beneficial, adaptive function, the consequence for respiratory variability is a disturbance from the optimal range, which then requires a sigh to reset it. Future research should delve into this relationship further by noting the effect of different inter-target intervals on entrainment and how this affects sigh frequency.

Finally, we show for the first time in humans that sighs are concurrent with changes in PD, implicating sighs as part of a noradrenaline-related arousal mechanism. Sighs have been seen to be noradrenaline dependent in mice (Viemari et al., 2013), and the locus coeruleus has been suggested as a key modulator in changing brain states following a sigh (Severs et al., 2022). From a wider perspective, our finding also provides another avenue of evidence for an inherent relationship between respiration and locus coeruleus – noradrenaline (LC-NA) activity. The pattern of PD activity over the sigh was different for each of our groups. In Grad, PD steadily rose over the whole period, whereas in the PACE groups, PD rose sharply and then decreased after the sigh peak. We saw in EC1 that both the stimuli and the breathing intervention highly entrained the pupil activity and so this may explain this difference. The PD response in PACE-IB was the largest, and it's intriguing to speculate that the compounded effect of stimuli *and* breath entrainment on PD may have pupil activity 'primed' and more responsive to large changes in respiration. It has been seen that respiratory volume is closely proportional to PD (Kluger et al., 2023; Ohtsuka et al., 1988), however, this group's sigh volume was not larger than NIB's and thus there appears to be an additional influence here. Another noteworthy aspect of the PD pattern for the PACE groups is an apparent dip after the initial increase. One possibility is that the initial increase is related to a noradrenergic trigger to induce a sigh, and the larger increase that follows is tracking the respiratory depth. More detailed analyses of PD and sigh behaviour during quiet rest should help to elucidate this.

In conclusion, whilst we corroborate previous findings that sighs are related to disturbances in respiratory variability, we additionally show that respiratory entrainment and altering task demands have significant influences on sigh frequency. Thus, the occurrence of sighs is sensitive, and possibly specific, to a given task due to factors not previously considered. In addition, sighs are concurrent with changes in PD which implicates the LC-NA arousal system in sigh behaviour, and more broadly, the respiratory system.

Thesis Discussion

The aim of this thesis was to investigate an interplay between respiration and attention. The breath is a fundamental tool in meditative practices where the primary aim is to enhance sustained attention capabilities, and this knowledge has been passed down for millennia. We now have the technology to interrogate this relationship in great detail using neuroscientific methodologies, and seemingly the motivation, considering the recent surge in interest of an interplay between respiration and cognition. Central to this investigation was the role the locus coeruleus–noradrenaline (LC-NA) arousal system could play in mediating between respiratory and attentional oscillations, building on primary support for this model (Melnychuk et al., 2018, 2021).

Thesis Contributions

Empirical Chapter 1 was a direct test of whether slow paced breathing (SPB) would stabilise attention as well as pupil diameter (PD) oscillations (as a proxy measure for LC tonic activity). This experiment revealed that, in comparison to spontaneously breathing controls, SBP mitigated attentional lapses in the task and additionally entrained PD to the frequency of the guided respiration.

These findings are of primary significance to the respiration-LC-attention dynamical systems model. This is the first direct test of a prediction from this model following the authors' initial evidence of synchronisation between these systems. The present evidence is in favour of the prediction of the model, with SPB participants showing evidence of remaining in a stable state of attention. Future research should aim to disentangle the effects of top-down attention control required to maintain an unfamiliar respiratory rhythm, and the bottom-up influence of respiration on the LC. This could be achieved either by recruiting participants who are familiar with breathwork, or alternatively, providing an appropriate control condition such as breath monitoring without manipulation. A further step would be to test the prediction in the other direction and have an additional group breathing intentionally more randomly and note if this is related to higher attentional lapses.

Secondly, these findings contribute to the mixed literature regarding a modulatory effect of respiratory rate on PD. A recent review (Schaefer et al., 2023) highlighted that there have been four studies to show evidence in favour and four against. Importantly, the latter group tended to have greater sample sizes (n > 15). The present sample size was relatively high and shows strong support for a modulatory effect of respiratory rate on PD. Besides one other (Daum & Fry (1981) also showed support), this is the only study to perform a direct test involving a respiratory manipulation. It is possible that a strong coherence is seen between respiration and PD only at specific frequencies, if there is, for example, resonance between respiration and another system, such as is the case for 0.1 Hz and the baroreflex (P. M. Lehrer & Gevirtz, 2014).

Or perhaps, stronger coherence occurs at frequencies lower than resting rate, the rate most commonly previously investigated (Schaefer et al., 2023). Additionally, the strength of coupling could be modulated by the goal-directedness of attention, that is, perhaps synchronisation between oscillators reaches a stable state when attention is geared towards a relatively constrained end. Future work should aim to experimentally control these factors for greater clarity.

An additional contribution of this study was the creation of a novel task. To our knowledge this is the second task to implement a guided breathing rhythm during a task (D’Agostini et al., 2022), and it was feasible to do so on both accounts. This opens up avenues for future research to explore an effect of respiratory rate on different aspects of cognition.

Finally, slow breathing has primarily been discussed in relation to reliably induced relaxation effects (Zaccaro et al., 2018). Physiological mechanisms such as decreased heart rate and increased heart rate variability likely play a large role in these effects (Shao et al., 2024; Zaccaro et al., 2018). However, it is also possible that stable attention driven via the LC-NA system could be playing a role in psychological relaxation too. That is, a consequence may be a less turbulent mind regarding the focus of thoughts. Although the efficacy of slow breathing is well established academically and anecdotally, the mechanisms are still unclear.

Empirical Chapter 2 used younger (YAs) and older adults (OAs) to assess how differences in attentional engagement are reflected in respiratory-task entrainment, how various attentional signatures are modulated over the respiratory cycle, and whether these modulation patterns can be contextualised in relation to entrainment. OAs, who showed evidence of higher attentional engagement also demonstrated greater respiratory-task entrainment. In both groups, self-reported task focus (experiential), reaction time (behavioural), PD and EEG-derived brain oscillatory activity (physiological) all showed significant modulation over the respiratory cycle. Attentional engagement (derived from age group differences) and respiratory-task entrainment appeared to have considerable, although differing, influences on the patterns of modulation, highlighting the role of top-down and bottom-up contributions. Finally, modulation patterns indicated that the signatures of attention were most optimal for task focus during the period of observed respiratory-task entrainment, and less optimal outside of this window.

There are a number of novel contributions of this study. Namely, it is the first investigation into any sort of inter-individual differences regarding respiratory-task entrainment. Additionally, it is the most comprehensive analysis of respiratory modulation of cognition, both in terms of the respiratory phase granularity of modulation tested and the span of measures used. It is the first report of a subjective measure being modulated over the respiratory cycle. Finally, it is the first study to directly contextualise respiratory modulation patterns to respiratory-task entrainment phases.

The specific modulation patterns observed of attentional signatures over respiratory phases were likely specific to the task used, the Gradual Contrast Change Detection – Experience Sampling Task. In particular, the continuous nature of the task compared to commonly used tasks containing only sudden-onset trials may have facilitated a relatively smooth modulation of attention, rather than a punctuated one. Qualities of specific respiratory phases were not of primary interest here, but rather, the idea that the respiratory cycle may provide opportune windows for attentional reallocation between task focus and mind wandering. It does appear as though participants utilised the interoceptive signal of respiration to guide their attention in this way, aligning environmental, physiological and behavioural oscillations to aid prediction of target occurrence and non-occurrence. This conclusion is consistent with the proposal that respiration acts as an informative prediction error signal within a predictive coding framework (Allen et al., 2023; Boyadzhieva & Kayhan, 2021; Brændholt et al., 2023). It is intriguing to speculate that the enhanced attentional abilities gained from ‘breath mindfulness’ could be derived from bringing greater understanding to when attention is likely to reallocate with respect to the respiratory cycle.

In this study, there was further support for a respiratory modulation of PD. In contrast to Empirical Chapter 1, there was no explicit respiratory manipulation, however, there did seem to be a considerable influence of respiratory-task entrainment driving this PD modulation effect. Thus, regularity in respiratory dynamics (through entrainment) is still implicated in stabilising PD oscillations. Significant PD modulation was still present albeit to a lesser degree in the OAs non-entrainers, which also highlights a stabilising role of top-down attentional engagement. The relative contributions of these driving factors in a respiratory-PD modulation relationship may help to explain variation in previous findings (Schaefer et al., 2023), and future experiments could be made with these in mind. In particular, the split of significant vs non-significant respiratory-task entrainers should be useful.

On this point, no study to date has sought to investigate why certain individuals entrain their respiration to tasks and others do not. A role of an individual’s attentional strategy is implicated here. Respiratory-task entrainment could actually prove useful as an attentional signature itself. However, this certainly does not explain all the inter-individual variability, and future research should investigate other potential factors such as interoceptive awareness of the respiratory signal. Additionally, future studies could experimentally manipulate inter-target intervals to understand what is conducive for entrainment. It is quite remarkable that participants in this study entrained to constantly changing inter-target intervals. Although, presumably this was still feasible due to the inter-target intervals (3, 5, 7 s) being approximate to the range for typical resting respiration (0.2 - 0.33 Hz; Sapra et al., 2024). It would be intriguing to note how entrainment is affected by adjusting the duration and variability of consecutive inter-target intervals. It may prove as a useful subperceptual respiratory manipulation.

Empirical Chapter 3 was an investigation into sighs, a key component of the respiratory rhythm believed to be crucial in maintaining optimal respiratory dynamics and levels of psychological stress (Severs et al., 2022; Vlemincx et al., 2022; Vlemincx, Van Diest, et al., 2010). Utilising data from Empirical Chapter 1 and 2, it was demonstrated across these two different paradigms that sigh frequency did relate to increasing randomness in respiratory variability, and that the effect of a sigh was to decrease this. Additional influences of task dynamism and respiratory entrainment on sigh frequency were also discovered. Sighs did not seem to affect task performance or subjective focus. Despite no behavioural or experiential consequence on attention, PD increased considerably over sighs, implicating the LC-NA arousal system here for the first time in humans.

The relation between sighs and arousal has been clearly suggested (Ramirez et al., 2013; Severs et al., 2022; Vlemincx et al., 2022), but direct evidence is lacking. The most direct evidence provided in this chapter is the effect seen on PD. Only one study so far, in mice, has made a link between NA and sigh occurrence (Viemari et al., 2013).

Consistent with the “reset” perspective of sighs, they may be implicated in resetting arousal. Presumably in the present, long duration, monotonous, sustained attention tasks, individuals would experience frequent drops in arousal and sighs may have provided an alertness boost. It would be intriguing to observe PD during highly arousing circumstances and see if it decreased, since sighs have been seen to provide relief after viewing negatively valanced, highly arousing images (Vlemincx et al., 2015). Presumably, there would still be an acute increase in PD over the sigh period, but PD may then settle to a lower baseline than before the sigh. Future studies should also test for differences in task performance or experienced arousal using other tasks to see if there is a perceptual alteration in arousal following a sigh.

It is highly interesting that respiratory entrainment was related to sighs. This implies that the presumably adaptive function of entrainment has maladaptive consequences to respiratory dynamics. The long-term maintenance of respiratory-task entrainment may be dependent on sighs and their ability to reset respiratory variability. If this relationship is confirmed, it should be integrated into the “resetter hypothesis” of sigh functioning (Severs et al., 2022; Vlemincx et al., 2022). Future research manipulating inter-target intervals may also prove as a useful, subperceptual manipulator of sigh frequency.

Limitations and Future Directions

Firstly, the scope of the present thesis is fairly limited insofar as it revolves around a model regarding the LC-NA arousal system. This is by no means the only likely pathway through which respiration is modulating cognition more broadly than attention. For instance, there is reason to believe that respiration has phase-phase and phase-amplitude coupling relationships with brain oscillations that do no rely on the LC pathway (Allen et al., 2023; Boyadzhieva & Kayhan, 2021; Brændholt et al., 2023). However, it is the lack of research into the LC pathway and consequences for attention that motivated the present work. In Empirical Chapter 2, evidence was found for phase-amplitude coupling between respiration and higher frequency activity in frontal and posterior regions. More comprehensive work could seek to not only consider these pathways in isolation, but how they interact. The respiration-LC-attention coupling could also be extended in its scope. The influence of other interoceptive signals could included in the model, starting with cardiovascular given the close association with the respiratory system. For example, Grund et al. (2022) found that tactile perceptive sensitivity was modulated by both the respiratory and cardiac cycle. Recent evidence suggests that the LC does indeed communicate with the heart (Lian et al., 2023). Simultaneous recording of respiration, heart rate and PD could prove insightful. A speculative idea for an investigation could be: respiratory sinus arrythmia is the effect of heart rate increasing during inhalation and decreasing during exhalation, perhaps the respiratory-phase modulation of PD could also be correlated to this effect. Additionally, what is occurring to PD when there are resonant effects between respiratory and cardiovascular systems during heart rate variability biofeedback breathing? There are also exciting avenues for expanding this model with a consideration of large-scale brain networks. Using functional magnetic resonance imaging (fMRI), it should be seen whether respiration modulates activity in, and coupling between, the default mode network, frontoparietal network and salience network, given their instrumental role in changing attentional states and how they can all be manipulated by LC activity. For example, the salience network, critical for monitoring visceral information from the body, can amplify respiratory signals back to the cortex, and potentially strengthen the coupling between respiration and putative cortical networks via the LC.

The present thesis did not explore the relative contributions of nasal versus mouth breathing with regards to how they affect brain activity (Arshamian et al., 2018; Jung & Kang, 2021; Price & Eccles, 2016) or the LC specifically. It was an intentional choice in the present experiments not to obstruct either breathing route, due to concerns of discomfort for participants, and because this would induce unnatural breathing patterns. However, future studies could measure relative airflow entering through each passage to disentangle effects by using non-invasive infrared thermography, which captures relative cooling during inhalation and heating during exhalation (Telson et al., 2023). Conclusions from research thus far favours a crucial role of the nasal pathway for entraining the olfactory bulb which in turn can modulate other brain regions (Heck et al., 2017; Juventin et al., 2023; Tort, Brankačk, et al., 2018; Zelano et al., 2016). However, with regards to the LC, it may not discriminate between nasal versus oral routes if it is only receiving information regarding respiratory rate via the preBötzinger complex or fluctuating CO_2 levels, or depth via vagal pulmonary afferents. Perhaps top-down respiratory information from the frontal regions to the LC could be affected by airflow route whereas bottom-up information would not. Regardless, it should be stated that mouth breathing is highly deleterious to health and should be discouraged (Alhazmi, 2022; Fitzpatrick et al., 2003; Jefferson, 2010; Lin et al., 2022; Ribeiro et al., 2016).

A key limitation is that LC activity is not directly accessed in present studies, but instead, PD was used as a proxy measure. As frequently cited in this thesis, it is believed to be a reliable proxy (Bang et al., 2023; DiNuzzo et al., 2019; Elman et al., 2017; Joshi et al., 2016; Meissner et al., 2023; Murphy et al., 2014). Of particular significance is the recent paper from Bang et al., 2023. The authors trained clinical depth electrodes *in vitro* to specifically identify noradrenergic activity which were then implanted in the amygdala of epilepsy patients since the amygdala receives dense LC projections (McCall et al., 2017). Amygdala stimulation in the study was targeted by participants performing an emotion task, and activity recorded from the electrodes was well correlated to pupil activity. Therefore, LC-NA output was tracked by PD changes. Another innovative recent study showed that participants could dilate or constrict their pupil size at will through biofeedback training (Meissner et al., 2023), with the degree of participants' pupil modulation being related to fMRI blood-oxygenation-level-dependent (BOLD) activity in the LC. Additionally, they showed that participants altering their baseline PD had consequences for the amplitude of their evoked PD as well as their reaction times in an auditory oddball task. This latter finding has relevance with regards to the balance between LC tonic (baseline) and LC phasic (evoked) activity. However, there still remains some dispute regarding PD as an accurate read out of LC activity. A recent study correlating LC activity and PD in mice reported that there was considerable variability in the reliability of this relationship despite constant stimulation, and PD may only reflect a minority portion of LC activity (Megemont et al., 2022). Additionally, changes in PD were seen to correlate with other areas near to the LC (Joshi et al., 2016), and NA may not be the sole modulator of PD (de Gee et al., 2017; Larsen & Waters, 2018). Overall, the evidence is in favour of PD being a reliable proxy measure for LC activity, however, further research in humans using innovative techniques like those used by Bang et al., (2023) and Meissner et al., (2023) should help clarify this. Further, such approaches should be applied to demonstrate a respiratory input to the LC in humans. It would be curious, for example, to note what happened to participants' respiration during PD self-regulation. The present thesis predominantly utilised PD in a relatively imprecise manner, measuring its oscillatory activity and deriving fluctuations in LC tonic level, rather than e.g., the precise timing of evoked LC phasic burst activity. Therefore, PD should have served as a sufficiently accurate proxy measure for this usage.

A limitation specific to Empirical Chapter 2 is the use of YAs and OAs to split participants according to attentional engagement. It is noted that these groups obviously differ in a number of other ways, such as motivational factors, their familiar with technology, but also potentially their LC integrity (Mather & Harley, 2016). All our OAs had to have a passing score on a standardised test of cognitive abilities and all task metrics except self-reported focus were comparable with the YAs. Thus, although an oversimplification, utilising these groups for the present purposes was likely appropriate. Future work should consider ways to determine a contribution of top-down attention on LC and respiratory activity with less confounding factors.

Suggestions for specific future research have been made throughout this Discussion. With regards to the larger picture, there is still lots of exciting research to be done in this emerging area.

What is known about the effects of breath control and breath mindfulness vastly outweighs the current understanding of the mechanisms behind these effects. Understanding these will not only help target therapies but will contribute to our understanding of how information is processed in the brain in a fundamental manner. Mounting evidence suggests that a full picture of cognition is incomplete without an understanding of how brain activity is influenced by signals from the periphery (Azzalini et al., 2019; Heck & Varga, 2023; Varga & Heck, 2017). The present evidence warrants further investigation into how respiration interacts with the LC-NA system considering the fundamental and pervasive nature of this system in arousal and attention. Further efforts should be made to “map” the respiratory cycle in terms of how different sensory-cognitive processes and attention are modulated across varying contexts to work towards a unifying framework of brain-body cognition. For example, performing a similar analysis to the resting state magnetoencephalography (MEG) imaging data from Kluger & Gross (2021), calculating modulation indices across the whole brain and across frequency bands using MEG imaging, but during cognitive tasks. Additionally, like was done presently in Empirical Chapter 2, efforts should be made to analyse task performance within smaller phase windows than ‘inhalation’ or ‘exhalation’ to understand the nuances of the whole respiratory cycle.

Future work should seek to understand how the LC-NA and respiratory systems develop together over long periods of time. Firstly, it should capitalise on the exceptional respiratory and attentional training that long-term meditators undergo. Predictions regarding the relative evolvement of top-down and bottom-up effects of meditation and pranayama respectively have been proposed by Melnychuk et al., (2018). Their conceptualisation from the dynamical systems perspective is that regular practice should strengthen the stability and depth of attractor basins. That is, stable states of attention should be more stable, allowing individuals to persist in these states for longer, and be less vulnerable to distractors. In the other direction, LC degradation is well documented in ageing studies (Betts et al., 2019; Mather & Harley, 2016), and simultaneously, the respiratory system loses its vigour (S. H. Lee et al., 2016; Sharma & Goodwin, 2006). It would be curious to note if there are consequent effects how these systems interact, and whether this can go some way in explaining the cognitive inflexibility in attention seen in OAs.

Understanding all of these mechanisms should be investigated in tandem with how to utilise this information for better health outcomes. For instance, if slow breathing does stabilise attention by inherent interactions with the LC-NA system, then therapies aiming to improve attentional abilities should target both systems for maximal effect, either in conjunction such as during meditation (Craigmyle, 2013), or intense breath regulation (Kox et al., 2014), or in isolation.

As alluded to in the Introduction of this thesis, our attentional capabilities are being stretched to their limit in modern society (Nations, n.d.). A greater understanding of how attention fluctuates for the typical individual in daily life and the relation to the respiratory cycle, may mitigate negative experiences like intense stress or burnout. For example, the term “email apnoea” was coined to describe an experience of breath holding whilst checking emails (*Just Breathe*, 2008). This is obviously not specific to emails, but it may reflect more broadly the damaging consequences for respiratory dynamics of the frequent attention reallocation that occurs during quick successive cognitive tasks that make up most peoples’ days in modern industrial society. Naturalistic studies with continuous respiration monitoring during every day tasks may highlight areas where attention in the short term and mental health in the long term are compromised.

Concluding Remarks

Collectively, the findings of the present thesis provide support to the idea that respiration and attention are interconnected. This connection was apparent over two different tasks, during spontaneous and volitional respiration. The LC-NA arousal system was implicated in each case, as well as during sighing, providing initial support for a dynamical systems model revolving around this system as a key nexus in a respiration-attention coupled relationship. These studies also demonstrate the utility of novel methodologies to investigate the role of respiration in cognitive neuroscience, contributing to an up-and-coming area with large implications for how the mind and body work to process the world around us. This investigation into material mechanisms linking respiration and attention also complement the longstanding experienced knowledge preserved by the yogis through the ages. The exploration of mechanisms for implicit interoceptive coupling between respiration and attention may offer crucial insights into understanding impairments of respiratory-attentional coupling, which play a pivotal role in impairments of embodied cognition across various clinical conditions. Failure to recognise key interoceptive cues from the breath could manifest as distressing symptoms, such as panic disorder and anxiety. The degree of respiratory-attentional coupling, including the flexibility of the system such as sigh resets, may prove to be useful biomarkers for embodied symptoms that transcend diagnostic boundaries.

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