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The Adaptive Brain: Temporal Processing, State Flexibility, and Chronic Stress in Dynamic Attending

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The Adaptive Brain: Temporal Processing, State Flexibility, and Chronic Stress in Dynamic Attending

A Dissertation submitted in partial satisfaction of the requirements
for the degree Doctor of Philosophy

in

Neurosciences

by

Gina Masego D'Andrea-Penna

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2024

The Dissertation of Gina Masego D'Andrea-Penna is approved, and it is acceptable in quality and form for publication on microfilm and electronically.

University of California San Diego

2024

EPIGRAPH

"We are our choices."

Jean-Paul Sartre

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LIST OF ABBREVIATIONS

ACh	Acetylcholine
ACC	Anterior cingulate cortex
ACM	Adaptive capacity model
ACTH	Adrenocorticotropic hormone
ADHD	Attention-deficit/hyperactivity disorder
ANB	Alternate nostril breathing
BAI	Beck Anxiety Inventory
bpm	breaths per minute
BSPAS	Burn-Specific Pain Anxiety Scale
CAN	Central autonomic network
CLEAR-NPT	Checklist to evaluate a report of a nonpharmacological trial
CO2	Carbon dioxide
CRF	Corticotropin-releasing factor
CVLM	Caudal ventrolateral medulla
DASH	Dietary Approaches to Stop Hypertension
DASS	Depression Anxiety Stress Scales
dB	Decibel
df	Degrees of freedom
DSM	Diagnostic and Statistical Manual of Mental Disorders
DVN	Dorsal motor nucleus of the vagus nerve
EEG	Electroencephalography
fMRI	Functional magnetic resonance imaging

HADS	Hospital Anxiety and Depression Scale
HPA	Hypothalamic-pituitary-adrenal
HRV	Heart rate variability
Hz	Hertz
IML	Intermediolateral nucleus
IOI	Interonset interval
ITI	Inter-tap interval
MBSR	Mindfulness-based stress reduction
MIND	Mediterranean-DASH Diet Intervention for Neurodegenerative Delay
mPFC	Medial prefrontal cortex
NA	Nucleus ambiguus
NE	Norepinephrine
NHLBI-NIH	National Heart, Lung, and Blood Institute of the National Institutes of Health
NST	Nucleus of the solitary tract
PFC	Prefrontal cortex
POMS	Profile of Mood States
PSS	Perceived Stress Scale
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analysis
RCT	Randomized control trial
REM	Rapid eye movement
RVLM	Rostral ventrolateral medulla
SCFA	Short-chain fatty acid
SD	Standard deviation

SMS	Sensorimotor synchronization
SNR	Signal-to-noise ratio
STAI	State Trait Anxiety Inventory
TRI	Timing response index
UNB	Unilateral nostril breathing
VAS	Visual Analog Scales
VS	Vector strength

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On a more personal note, I would also like to thank my parents, who have nurtured my curiosity and who always encourage me to pursue my passions. I am incredibly grateful for Holly (Yueying) Dong, who started as my undergraduate assistant but has since become my best friend and fellow graduate student. Lastly, I would like to thank Gilberto Acevedo for his constant support. This past year has been challenging – to say the least – and I would not have made it through without him by my side.

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Chapter 2 contains unpublished material coauthored with Chiba, Andrea. The dissertation author was the primary author of this chapter.

Chapter 3 contains unpublished material co-authored with Chiba, Andrea A; Khalil, Alex K; Iversen, JR; Minces, VH. The dissertation author was the primary author of this chapter.

Chapter 4, in full, is a reprint of the material as it appears in *Brain Sciences*. Bentley TGK, D'Andrea-Penna G, Rakic M, Arce N, LaFaille M, Berman R, Cooley K, Sprimont P. 2023. Breathing Practices for Stress and Anxiety Reduction: Conceptual Framework of Implementation Guidelines Based on a Systematic Review of the Published Literature. Brain Sci. 13:1612. The dissertation author was the secondary investigator and author of this paper.

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2020 **D'Andrea-Penna GM**, Iversen JR, Chiba AA, Khalil AK, Minces VH. 2020. One Tap at a Time: Correlating Sensorimotor Synchronization with Brain Signatures of Temporal Processing. Cereb Cortex Commun. 1:tgaa036.

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ABSTRACT OF THE DISSERTATION

The Adaptive Brain: Temporal Processing, State Flexibility, and Chronic Stress in Dynamic Attending

by

Gina Masego D'Andrea-Penna

Doctor of Philosophy in Neurosciences

University of California San Diego, 2024

Professor Andrea Chiba, Chair

The ability to shift our internal state to meet expected environmental demands fundamentally molds our experience of and interaction with the world, supporting learning, speech comprehension, and social behaviors. Such dynamic attending relies on *(1)* temporal expectations to guide neurobehavioral state shifts and *(2)* sufficient state flexibility to allow for these shifts.

When the latter goes awry, we may struggle to increment our attention when faced with challenge or decrement arousal despite quiescent conditions. Whereas previous literature on dynamic attention emphasizes the role of temporal expectancy, little research examines the interplay between state flexibility and temporal processing. The present thesis aims to fill this gap in scientific knowledge by addressing both temporal processing and state flexibility in relation to dynamic attention. To do so, we measure sensorimotor synchronization and brain responses to rhythmic auditory stimuli to examine temporal processing, whilst considering the influence of diverse stressors on one's ability to shift states via self-reported lifestyle factors and emotional wellbeing.

In an experiment using both behavior and electrophysiology, Chapter 1 identifies a potential neural marker of auditory temporal processing. Chapter 2 subsequently provides an integrative review elucidating the influence of psychological and physiological stressors on brain state and state flexibility through allostasis. Chapter 3 then lends support to the arguments outlined in Chapter 2, describing an experiment in which chronic stress burden was found to correlate with resting cortical state. Lastly, a collaborative systematic review in Chapter 4 highlights the therapeutic potential of voluntary regulated breathing as a means of stress-reduction. Cumulatively, this research emphasizes the importance of neurobehavioral state flexibility in dynamic attention and its modulation by varied stressors. This synthesis illuminates the extensive yet underappreciated interconnectedness of brain, body, and behavior and urges a reconceptualization of stress, health, and the brain to lead future research and application.

INTRODUCTION

The ability to shift our internal state to meet external demands is crucial for adaptive behavior. For instance, during more primitive times, increasing one's arousal in a hostile environment facilitated swift detection of and response to predators, thus enabling survival. While imminent physical threats are less prevalent today, our rapidly changing environment continually taxes our adaptive capacity. Modern man rarely fights a lion but can immerse himself in diverse virtual worlds with a mere touch of his fingertip, swiping through games, videos, images, and messages within seconds. Outside of technology, matching our internal neurobehavioral state to the environment allows for fluid social interactions (Schirmer et al. 2016), speech comprehension (Assaneo et al. 2019), and sensorimotor synchronization (Repp 2005).

In an ever-changing environment, reactive shifts in internal state are untimely, often occurring *too late*. Instead, anticipatory adjustments in state to expected environmental demands prove more adaptive. *Allostasis*, a brain-centered mechanism of predictive regulation, offers a means through which these anticipatory adjustments can take place (Sterling and Eyer 1988; Schulkin and Sterling 2019). Specifically, after integrating various signals reflecting internal and external milieus, the brain recalibrates the system to meet projected demands.

Intrinsic to many of these predictions is temporal processing and expectancy, as many environmental events occur rhythmically or quasi-rhythmically. Perceiving these temporal regularities allows us to more accurately predict future stimuli and alter our state accordingly. Involving second and sub-second shifts in arousal, dynamic attention represents the finest grain instance of predictive state fluctuations that most prominently mediates our experience of and interaction with the world (Jones and Boltz 1989; Nobre and van Ede 2018). Through dynamic attention, we can enhance perception of important regular events, filter out irrelevant stimuli, and detect potentially rewarding or threatening unexpected events.

Temporal expectancy is necessary, but not sufficient, for dynamic attending. That is, one may be capable of predicting when an event will occur yet struggle to shift their internal state. Such state inflexibility can arise from neurophysiological adaptations to chronic stress or arousal, mediated by the same allostatic mechanisms supporting state shifts. Allostatic states of high arousal may enable appropriate responses to acute stressors but exact a toll in the long-term (McEwen and Stellar 1993); and the transition from acute to chronic arousal induces rigidity due to functional and structural changes in the brain and body. While this change in baseline state is not permanent, behavioral and/or environmental modifications are needed to reduce chronic arousal and regain state flexibility.

The integrated organismic system underlying allostasis involves bidirectional signals between the periphery and the brain, such that both physiological and psychological stressors engage allostatic machinery. As a result, chronic high arousal can result from not just anxiety or psychogenic stress but also from health risk behaviors, such as poor sleep, low-quality diet, physical inactivity, and excessive technology use (Dienlin and Johannes 2020; Suvarna et al. 2020). Moreover, these diverse stressors converge on the same system and cumulatively contribute to an allostatic load that wears on the brain and body (McEwen and Stellar 1993; McEwen 2017).

The recent COVID-19 pandemic served as a microcosm illustrating the cumulative effects of diverse chronic stressors (Zvolensky et al. 2020). Uncertainty, anxiety, and social isolation accompanying pandemic lockdowns deleteriously affected mental health (Rogers et al. 2021; Vindegaard and Benros 2020). Meanwhile, the profound disruption of day-to-day living encouraged sedentary behavior (Stockwell et al. 2021), consumption of ultra-processed foods

(González-Monroy et al. 2021), and greater reliance on technology (Popescu et al. 2022). Although lockdowns have ceased and outbreaks have largely subsided, the pandemic's impact has lingered throughout our transition to a "new normal" (Gallego Hiroyasu et al. 2023; Horita et al. 2022).

The present thesis aims to bridge our understanding of temporal processing and allostasis as interdependent contributors to dynamic attention. In an experiment using rhythmic tapping alongside passive listening with electroencephalography (EEG), Chapter 1 identifies a passive neural marker of temporal processing. Subsequently, Chapter 2 provides an integrative review elucidating the influence of modern-day psychological and physiological stressors on brain structure, function, and state. A second experiment, conducted post-pandemic, is described in Chapter 3. There we find an association between allostatic load, measured as cumulative stress burden due to poor lifestyle choices and emotional wellbeing, on cortical state indexed by resting-state oscillatory activity. Lastly, in a collaborative systematic review, Chapter 4 highlights the potential of voluntary regulated breathing as a means of stress- and anxiety-reduction.

With this synthesis, I hope to illuminate the extensive yet underappreciated interconnectedness of brain, body, and behavior. Through the lens of allostasis, we can begin to understand the profound impact of day-to-day behaviors on our neurophysiology and dissolve the artificial dichotomy between the mental and physical. Collectively, these insights call for a paradigm shift in our conceptualization of health, stress, disease, and the brain.

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Chapter 1 ONE TAP AT A TIME: CORRELATING SENSORIMOTOR SYNCHRONIZATION WITH BRAIN SIGNATURES OF TEMPORAL PROCESSING

Abstract

The ability to integrate our perceptions across sensory modalities and across time, to execute and coordinate movements, and to adapt to a changing environment rests on temporal processing. Timing is essential for basic daily tasks, such as walking, social interaction, speech and language comprehension, and attention. Impaired temporal processing may contribute to various disorders, from ADHD and schizophrenia to Parkinson's disease and dementia. The foundational importance of timing ability has yet to be fully understood; and popular tasks used to investigate behavioral timing ability, such as sensorimotor synchronization (SMS), engage a variety of processes in addition to the neural processing of time. The present study utilizes SMS in conjunction with a separate passive listening task that manipulates temporal expectancy while recording electroencephalographic data. Participants display a larger N1-P2 evoked potential complex to unexpected beats relative to temporally predictable beats, a differential we call the timing response index (TRI). The TRI correlates with performance on the SMS task: better synchronizers show a larger brain response to unexpected beats. The TRI, derived from the perceptually driven N1-P2 complex, disentangles the perceptual and motor components inherent in SMS and thus may serve as a neural marker of a more general temporal processing.

Keywords: electroencephalography (EEG), rhythm, sensorimotor synchronization (SMS), sensory integration, timing

Introduction

Temporal structure provides a foundation for our experience of and interaction with the world. By developing temporal expectancies of stimuli in our environment, we prepare our attention and behavior appropriately (Jones and Boltz 1989). We can modulate our vigilance to co-occur with particular predictable events (Jones and Boltz 1989); we can coordinate our bodily movements over time and through space; we can parse and comprehend speech (Assaneo et al. 2019); and we can reorient to unexpected, potentially dangerous stimuli. Temporal processing exists through both conscious and early, low-level predictive processes and consequently offers a basis for perception and behavior. Furthermore, some have suggested that the brain's ability to habituate to unimportant repeated stimuli and to orient to sudden changes (termed "neural adaptability") reflects an energy-efficient strategy and allows fluid behavior in a changing environment (Schafer 1982; Záborszky et al. 2018). Understanding the neural basis of temporal processing thus may yield insight into human perception, action, and cognition.

Sensorimotor synchronization (SMS), the coordination of one's movements with an external rhythm (Repp 2005; Repp and Su 2013), has been commonly employed to investigate timing ability in a number of experiments. Such studies, often exploiting the simplicity of finger tapping, reveal the role of temporal processing in a variety of abilities and pathologies: attention and ADHD (Khalil et al. 2013), speech processing (Corriveau and Goswami 2009; Tierney et al. 2015; Zhao and Kuhl 2016), schizophrenia (Carroll et al. 2009; Papageorgiou et al. 2013), Parkinson's disease (Roalf et al. 2018), and dementia (Rabinowitz and Lavner 2014), among others.

Because SMS involves both sensory and motor components, individual variation in synchronization may arise from differences in motor ability or from differences in the neural processing of time; and different paradigms are required to disambiguate the two. A neural index of passive temporal processing could serve as a potential solution by disentangling temporal from motor execution. Electroencephalographic (EEG) experiments examining interval timing and rhythm suggest the N1-P2 complex to be a promising candidate due to its modulation by temporal expectancy (Schafer et al. 1981; Lange 2009; Todorovic and de Lange 2012; Kononowicz and van Rijn 2014; Duczu 2019; Duczu et al. 2019; Menceloglu et al. 2020). The N1-P2 complex, a brain evoked potential (EP) elicited by stimulus onsets, offsets, and change, reflects early sensory processing (Näätänen 1990; Remijn et al. 2014). This EP has been used to estimate auditory threshold in adults (Lightfoot 2016) and may be influenced by top-down attentional mechanisms (Hillyard et al. 1973; Parasuraman 1978). Moreover, the amplitude of the N1 may correspond to conscious perception, with larger amplitudes suggesting greater subjective obtrusiveness of a stimulus (Näätänen 1990). Accordingly, the present study examines the relationship between the N1-P2 complex and SMS, evaluating the potential of the N1-P2 to serve as a neural marker of timing ability and a window into the means by which temporal expectancy impacts the subjects' ability to coordinate their actions with the dynamics of the environment.

The current experiment is thus designed to assess timing ability and to manipulate temporal expectancies. Participants first attempted to synchronize their tapping with an external beat on drums allowing digital recording. Subsequently, they partook in a passive listening task during which EEG was recorded: we adopted a temporal auditory oddball paradigm to measure neural responses to low-probability ("unexpected") beats inserted within a stream of isochronous beats. In a previous study Ford and Hillyard (1981) compared evoked responses to unexpected beats relative to expected beats in an isochronous stream. While differences were observed, their study compared brain responses to beats with short and long interonset intervals (IOI's); this approach conflates responses to broken temporal expectancies with the effect of sensory adaptation, a phenomenon in which responses to stimuli preceded by short IOI's are smaller than responses to stimuli preceded by long IOI's (Rothman et al. 1970). Our study intentionally evades differences in sensory adaptation to isolate the effect of temporal prediction on the N1-P2: we analyzed the neural response to a sound embedded in an identical local context in two conditions, one where it is unexpected and the other where it is expected, as determined by the global temporal context (see methods). We hypothesized that better synchronizers would exhibit a larger N1-P2 complex to deviant beats.

Materials and Methods

Participants

Thirty-five participants between ages 18 and 24 (mean 19 years, 20 female and 15 male) were recruited from the University of California, San Diego. One participant was excluded from the analysis due to excessive noise and artifacts in their EEG data, resulting in too few trials (< 80) after artifact rejection. For efficiency and as part of a larger group dynamics experiment, all sessions were conducted in groups of three, with the exception of three dyads. However, the tasks relevant to the present study entailed no explicit interactions between participants.

Stimuli & Procedure

For both the tapping task and passive listening session, participants heard rhythmic streams of tone bursts from a speaker (~75 dB, SPL). Each burst consisted of an 800-Hz sine pulse, 50 ms in duration with a 10-ms ramp up and ramp down to avoid clicks at onsets and offsets. All auditory stimuli and analog triggers were presented--and tapping recorded--using Adobe Audition with a Focusrite Scarlett 18i20 audio/digital interface with a sampling rate of 44.1kHz. Stimulus presentation with a powered JBL studio monitor introduced a 3-ms latency. The auditory stimuli were sent to the speaker through one of the output channels of the audio digital interface. On another output channel, we sent a simultaneous analog trigger. The analog trigger was collected through one input channel of the audio digital interface, together with the activity from the piezoelectric elements that were glued to the tapping boards. With this configuration, the triggers and participants' actions were collected simultaneously. Thus, the signals that we used for analysis were synchronized with a precision of one sample (i.e., less than a millisecond).

Tapping

Participants first tapped individually for one minute to isochronous beats. For the tapping task, beats were separated by a 600-ms interonset interval (IOI), a relatively comfortable pace for sensorimotor synchronization (Repp 2005). Beats were occasionally omitted (15% probability); however, participants were instructed to maintain the basic rhythm while tapping and to tap where the beat *should be*, despite the omissions. Participants tapped onto wood blocks affixed to drums at approximately lap height, under which piezoelectric sensors were placed to record their taps as digital audio files into Adobe Audition.

Passive Listening

A 30-minute passive listening session followed the tapping task (Figure 1.1). To avoid the confound of sensory adaptation, in which EP amplitude decreases with shorter IOI's (Rothman et al. 1970), we developed a two-condition paradigm consisting of two trial types that were presented alternately 8 times (for a total of 16 trials). The "long condition" used an 800 ms IOI, with rare extra beats occurring at a 400 ms IOI (halfway between surrounding 800-ms IOI beats, 15% probability). The "short condition" used a 400-ms IOI, with rare omissions (15% probability). These two conditions strategically allowed for identical stimulus sequences in which the same two IOI's preceded the key sound to which the evoked brain response was measured (either an extra beat in the long condition or a standard in the short condition), controlling for adaptation such that only their expectancy differed. Henceforth the extra beats in the long condition will be referred to as "deviants" and the sequence-matched, expected beats in the short condition will be called "standards."

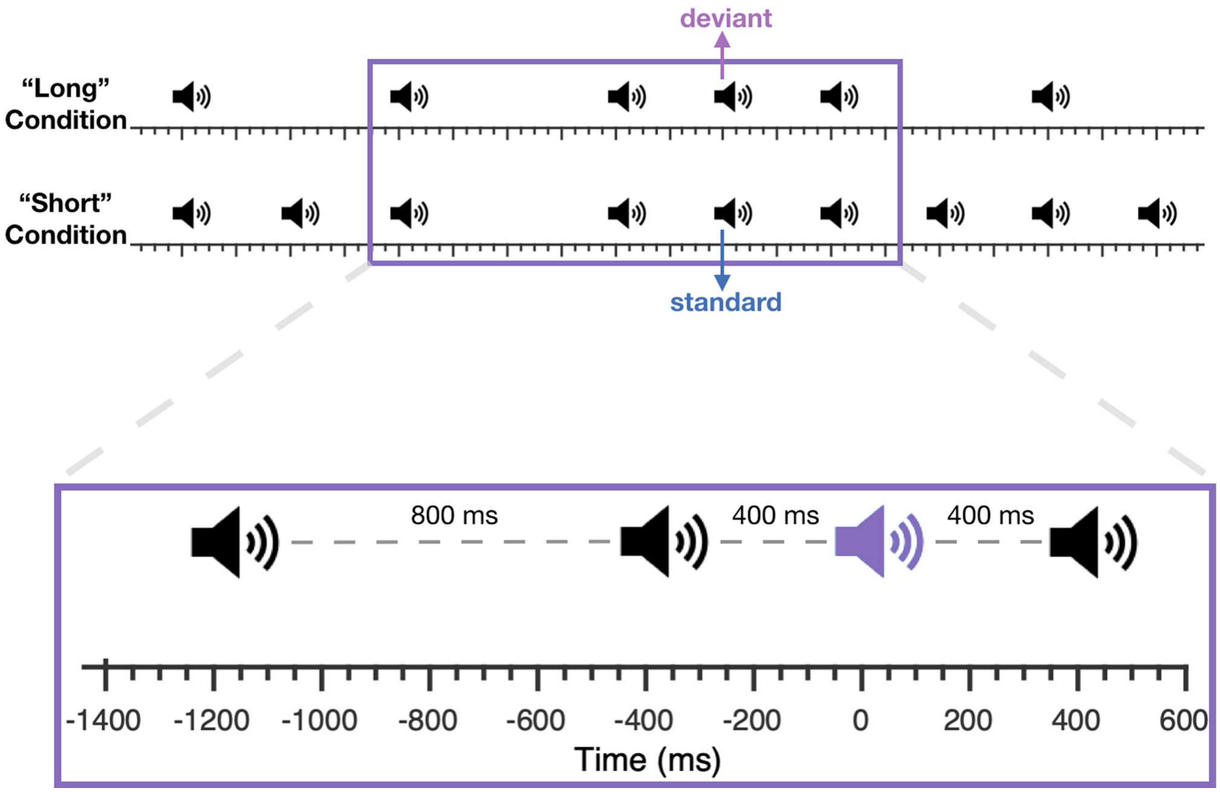

Figure 1.1: Passive listening temporal oddball paradigm. Participants passively listen to streams of sounds in two conditions. The "long" condition includes isochronous beats that are sometimes interrupted by an unexpected beat (deviant). The "short" condition is twice as fast as the long condition and contains occasional omissions. This arrangement allows us to compare brain responses to deviants and standards, which are physically the same sequence of stimuli to control for neural adaptation (see methods) but vary in temporal expectancy.

EEG Acquisition

During passive listening, participants wore custom, 5-channel dry EEG headsets containing electrodes at Fp1, Fp2, Cz, O1, and O2 (Cognionics, San Diego, CA; Chi et al. 2013, see Figure 1.2). Two frontal electrodes served as ground, and EEG data was referenced to the left earlobe. The headsets employ flexible plastic sensors with tines that penetrate hair to contact the scalp and active Ag/AgCl electrodes. Each headset was connected to a laptop using a USB isolator and running Cognionics Data Acquisition software. Cz was positioned approximately at vertex, and alcohol pads were used to clean participants' foreheads and other electrode sites when necessary. Signal quality was inspected prior to recording: all impedances were below 400 kΩ, with most below 300 kΩ. Square-wave triggers, with variable amplitude serving as event codes, were sent into the headset as analog input and recorded as an additional channel. Data was recorded at 4000 Hz to preserve the onsets of the triggers.

Figure 1.2: EEG equipment. Mobile, dry EEG headsets designed by Cognionics and employed to collect neural data.

Analysis

Tapping

An average of 122 taps was recorded per participant (range = 99 to 136). Tapping time series underwent a vector strength (VS) analysis, which provided a measure of each participant's ability to synchronize with the external rhythm -- particularly of their ability to tap with a consistent phase relative to the driving beat. VS is defined as:

$$\boldsymbol{VS} = \frac{\mathbf{1}}{\boldsymbol{N}} \left| \sum_{j=1}^{N} e^{i\,\phi j} \right|$$

Where N is the total number of taps by one participant, ϕj is the tap phase relative to the driving rhythm for tap number j, and i is the imaginary unit. Accordingly, VS is 1 if a tapper is perfectly consistent, maintaining the same phase across taps, and 0 if the participant taps randomly (Khalil et al. 2013). Circular standard deviation was also computed and yielded comparable results in the later correlational analyses.

EEG

Preprocessing

EEG data was processed and analyzed using EEGLAB (Delorme and Makeig 2004). We used data from Cz, consistent with previous studies examining the N1-P2 complex (Hillyard et al. 1973; Parasuraman 1978; Shafer et al. 1981). After identifying the different types of events (standard and deviant beats) using the amplitude-coded square waves from the trigger channel, data were downsampled to 500 Hz. A low-pass Hamming windowed sinc FIR filter with a cutoff frequency of 30 Hz was applied to the data prior to event selection and epoching. The deviant and standard beats (see Figure 1.1) -- were selected, epoched, and baseline corrected to the 50 ms period preceding the beat. Initially there were 169 deviant events and 185 standard events for each participant. Automatic artifact rejection via extreme values removed trials with voltages beyond ∓100 μV, leaving a mean of 156 deviants (range 88-169) and 170 standards (range 81-185) per participant.

N1-P2 EP Identification

Across-participant grand averaged EPs were computed for the deviant and standard beats separately, and the resulting N1 and P2 for each event type were used to determine time windows for calculating mean amplitude measures in single participants' EPs. Mean amplitude was used rather than peak values to bypass the influence of noise on single voltage values (Luck 2014); and separate time windows were examined for deviant and standard events, as N1-P2 latencies for the standard beat were generally earlier than those for the deviants (visible both in the grand average EP and in individual EPs; see Figure 1.3 for grand averages). Time windows +/- 50 ms surrounding the grand average peak for each condition were identified. Accordingly, the N1 mean amplitude for each participant was calculated between 72 and 172 ms and between 88 and 188 ms for the standard and deviant beats, respectively. The P2 mean amplitude was calculated between 124 and 224 ms for the standards and between 166 and 266 for the deviants. The N1-P2 magnitude was obtained by subtracting the N1 mean amplitude from the P2 mean amplitude, and a within-participant "difference magnitude" was calculated by subtracting the standard N1-P2 magnitude from the deviant N1-P2 magnitude. To evaluate the robustness of our findings using this difference magnitude measure, we both varied the window widths (+/- 20 and +/- 30 ms) and identified participants' peaks. For the latter analyses, the N100 and P200 for each participant were determined as the minimum and maximum voltages between the time windows defined for mean amplitude, respectively. Difference magnitudes were then computed using these peaks as well as using the mean voltage 20 ms around these peaks.

Statistics

The N1-P2 difference magnitude values between the deviant and short beats were correlated with solo tapping VS scores, using Spearman to account for non-normality and skew in VS scores. Supplementary analyses correlated the N100 and P200 magnitudes individually with VS and correlated the N1-P2 difference magnitude for each condition with VS. One-tailed t-tests comparing the N1-P2 magnitudes in the deviant and standard conditions and comparing the difference magnitudes of the 10 best and 10 worst synchronizers were conducted; we selected one-tailed t-tests because we hypothesized that deviant beats would elicit a larger N1-P2 and that this increase in magnitude would correspond to tapping ability, as better temporal prediction may underlie both measures. While the t-test comparing the best and worst tappers is redundant following the correlational analyses, it accompanies a plot which allows for a better visualization of our findings.

Data and Code. Data and Matlab code for the analyses can be accessed at https://github.com/victormінces/TRI.

Results

N1-P2 to Deviants v. Standards

To examine whether deviant beats elicit a larger N1-P2 than standard beats, we analyzed the N1-P2 magnitude to these types of stimuli. Consistent with dynamic attending theory (Jones and Boltz 1989) and the notion of neural adaptability (Schafer 1982), the N1-P2 magnitude to deviant beats (mean = 2.28, SD = 2.02) across subjects was larger than the N1-P2 to standard beats (mean = 0.36, SD = 1.19). This difference was statistically significant (paired one-tailed t-test, p = 1.22e-07, t-stat = 6.47, df = 33), indicating that unexpected beats elicit a larger N1-P2 than their expected counterparts (Figure 1.3).

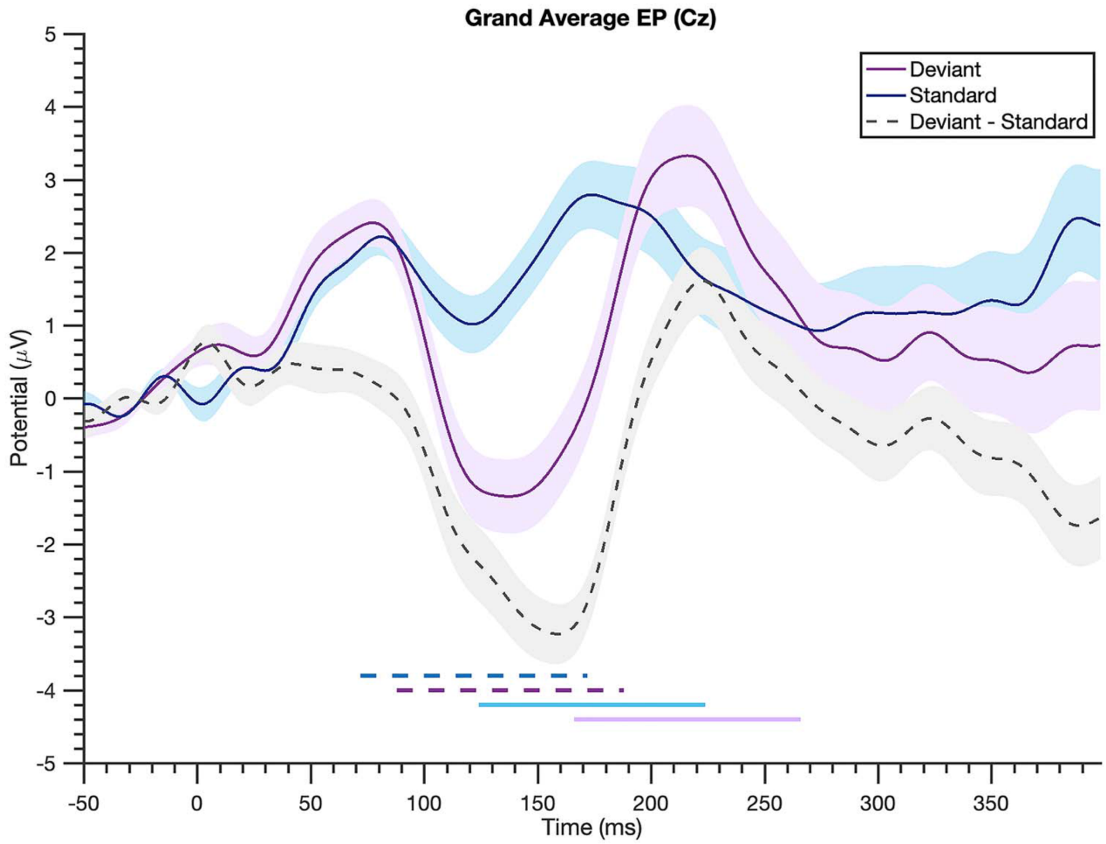

Figure 1.3: Grand average evoked potential is larger to deviant beats. Evoked potentials averaged across all participants (*deviant* = unexpected beat in "long" condition, *standard* = expected beat in "short" condition, shading = standard error). The N1-P2 complex (a negative-going deflection around 100 ms post-stimulus and the following positivity) is noticeably larger to the deviant beats relative to the standards, as seen in the gray dashed difference wave. The horizontal lines at the bottom indicate the time windows used for mean amplitude measures: dashed dark blue for the standard N1, dashed purple for the deviant N1, solid light blue for standard P2, and solid light purple for deviant P2.

Vector Strength

VS was used to assess the ability to synchronize with an external rhythm. The mean and median values for VS were 0.82 and 0.89, respectively, with a standard deviation of 0.187. VS scores were not normally distributed (p = 0.0017, Lilliefors's test statistic = 0.198) and were left skewed (-1.5 skewness).

Correlation between N1-P2 Response & VS

The N1-P2 difference magnitude significantly correlated with VS (Spearman's $\rho = 0.61$, $p = 1.79\text{e-}04$): individuals with larger N1-P2 mean amplitudes to the deviant beat had higher VS scores (Figure 1.4). That is, better synchronizers tended to have larger N1-P2 components to deviants. This correlation withstood a variety of manipulations, using shorter mean amplitude window widths (60-ms window, $p = 0.02$; 40-ms window, $p = 9.74\text{e-}05$), computing the N1-P2 difference magnitude with N1 and P2 peak voltages ($p = 0.045$) and averaging 20-ms windows surrounding individual participants' peaks ($p = 0.015$), and including musical experience as a covariate ($p = 8.21\text{e-}04$). Comparing N1-P2 difference magnitudes in participants with the 10 highest and 10 lowest VS scores yielded comparable results (one-tailed t-test, $p = 1.25\text{e-}04$, t-stat = 4.55, df = 18): those with the highest VS scores had larger N1-P2 difference magnitudes than those with the lowest VS scores (Figure 1.5), further illuminating the prior correlation. Upon examining the standard and deviant N1-P2 magnitudes separately, only the deviant N1-P2 magnitude significantly correlated with VS ($\rho = 0.43$, $p = 0.013$ for the deviant; $\rho = -0.18$, $p = 0.30$ for the standard), suggesting the effect is indeed driven by a larger N1-P2 to the deviant beat. Moreover, correlating the N1 magnitude and P2 magnitude individually with VS revealed that neither component alone is responsible for these findings ($\rho = -0.11$, $p = 0.5$ for the former and $\rho = 0.3$, $p = 0.08$), an observation reinforced by a significant correlation between N1 and P2 magnitudes ($p < 0.01$ for both the deviant and standard, as well as for their difference).

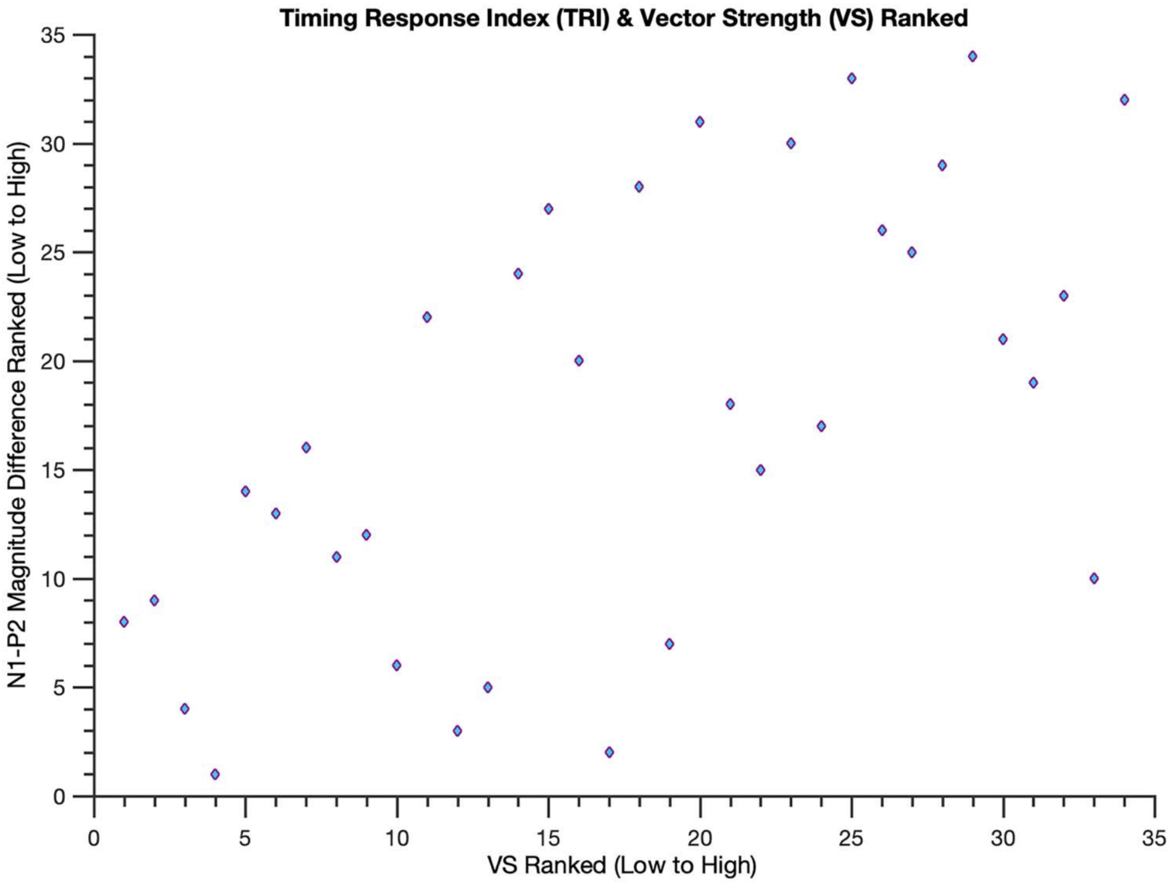

Figure 1.4: Brain responses to unexpected beats predict better sensorimotor synchronization. Lower VS values indicate poor synchronizing skills, lower TRI values indicate that the brain responses to unexpected beats are similar to expected beats. Scatterplot of ranked VS and TRI values. Better synchronizers (i.e., participants with higher VS scores) tend to exhibit a larger TRI (Spearman's ρ = 0.61, i.e., a larger N1-P2 to deviant beats; p = 1.79e-04).

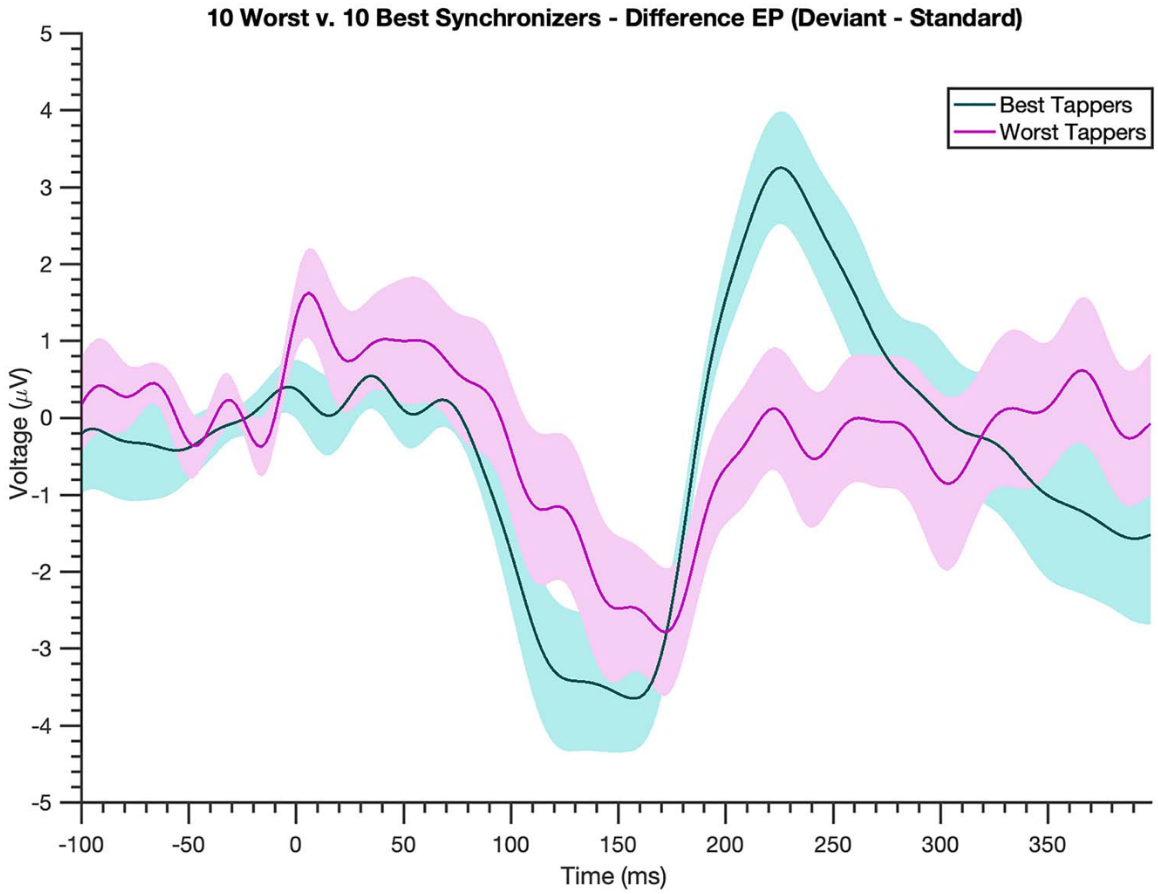

Figure 1.5: Top synchronizers show a larger brain response to deviant beats. Difference wave (EP to deviant beat - EP to standard beat, shading = standard error) for the best 10 synchronizers (teal) and worst 10 synchronizers (magenta) determined by VS scores. The best synchronizers exhibit a much larger N1-P2 complex to deviant beats compared to the worst synchronizers.

Discussion

Our results reveal a larger N1-P2 complex to deviant beats and find individual differences in this N1-P2 modulation to correlate with tapping ability measured as VS: participants with a larger N1-P2 to deviant beats tapped more synchronously with an external beat. Overall, the larger N1-P2 complex to deviant beats is consistent with a variety of studies utilizing oddball paradigms (Ford and Hillyard 1981; Menceloglu et al. 2020), examining other temporal expectancy effects (Schafer et al. 1981; Lange 2009; Todorovic and de Lange 2012), and investigating interval timing

(Kononowicz and van Rijn 2014; Duczu 2019; Duczu et al. 2019). We propose that our N1-P2 difference measure defines a timing response index (TRI).

Of greater interest is that the TRI predicts individual differences in tapping ability. The N1-P2, indicative of sensory processing, allows us to dissociate the sensory and motor aspects of temporal processing that are conflated in sensorimotor synchronization (SMS). It is important to emphasize that the EP data analyzed was collected during a passive temporal auditory oddball session, separate from the active tapping task. Correspondingly, neural processing that occurs passively, reflecting the ability to detect temporal regularities in the environment, has significant implications for behavior. Maintaining SMS requires significant and continuous multisensory integration of information of different latencies and temporal resolution. The TRI, consequently, may serve as a neural marker of more generalized temporal processing, which may prove useful both theoretically and clinically, pending future empirical investigation

It is possible that the TRI originates from other overlapping EEG components, such as the mismatch negativity (MMN), which may augment the N1. Yet, because the MMN has relatively poor signal-to-noise ratio and low intra/inter-subject reliability (Martin and Boothroyd 1999; Jones et al. 2000; Cone-Wesson and Wunderlich 2003), it is somewhat unlikely that this component accounts for our findings. Regardless, the predictive utility of the TRI endures whether it represents a genuine N1-P2 complex or some other component, and further research is required to assess its specific underlying brain potentials. Despite this qualification, our strategic passive listening paradigm circumvents the problem of sensory adaptation, in which shorter interonset intervals in repeated stimuli elicit smaller neural responses such as the N1: we compare key beats (either labeled “deviants” or “standards”) that are preceded by the same sequence of stimuli and differ only in expectancy. The TRI thus cannot relate to differences in the physical stimuli themselves.

The TRI may signal the degree to which a given beat is detected as violating its temporal context. Such a violation requires additional processing, resulting in a cascade of incrementing attention, learning and plasticity for the purpose of updating perceptual predictions. Greater sensory processing of, and attention to, less expected events may constitute an evolutionarily adaptive phenomenon requisite for learning, as such events may pose a threat or opportunity (Oros et al. 2014). In contrast, when innocuous stimuli, like the standard beats, are repeated, it would be neurally and behaviorally more efficient to reduce processing and perception of them unless they are task-relevant. This supposition is also consistent with the musicological theory that intentional irregularity in music drives audience engagement and musical affect (Keil 1995). The coordination of temporal processing with perception, attention, and learning facilitates a more energetically economical and behaviorally efficacious means of interacting with our environment: we can either “tune in to” or “tune out” predictable stimuli while updating our expectancies to incidentally detected changes in the environment (Khouri and Nelken 2015).

Employing a tapping task and passive temporal auditory oddball paradigm, our study found that individuals with a larger N1-P2 complex to unexpected beats synchronized more adeptly with a driving rhythm. The N1-P2, associated with low-level sensory processing, may potentially signify the means by which temporal expectancy influences perception and contribute to our neural marker of temporal processing, the timing response index (TRI). The rhythmic auditory task places no overt requirements on the subjects, requiring only passive listening, making the TRI particularly well suited for studying time processing in diverse populations (Kraus and Nicol 2017). For example, the TRI may facilitate the identification of temporal processing deficits clinically, both in communicative, compliant adults and in noncompliant or vulnerable populations with compromised attention, cognition, behavior and/or language (Carroll et al. 2009; Corriveau and Goswami 2009; Khalil et al 2013; Papageorgiou et al. 2013; Rabinowitz and Laven 2014; Roalf et al. 2018). Furthermore, examining the TRI in individuals trained to improve SMS may provide insight into the processes underlying such improvement. The reported correlation between the TRI and timing ability offers a variety of avenues to further explore the neural predictive processes crucial to motor coordination, dynamic attention, and cognition.

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Chapter 2 ALLOSTATIC LOAD, LIFESTYLE, AND NEUROBEHAVIORAL STATE FLEXIBILITY: AN INTEGRATIVE REVIEW

Arousal Fluctuations at Diverse Timescales

The brain and body are characterized by episodic fluctuations occurring at a variety of nested timescales. For instance, seasonal shifts in mood arise from changes in weather (Keller et al. 2005); cognitive and emotional changes accompany the menstrual hormonal cycle (Farage et al. 2008); arousal fluctuates with daily circadian rhythms (Dijk et al. 1992); and ultradian events influence performance approximately every 90 minutes (Hayashi et al. 1994). At finer second-to-second and millisecond timescales resides dynamic attention, in which periodic changes in attentional state support perception of and interaction with the external world (Shalev et al. 2019). These diverse fluctuations are shaped by a combination of ongoing endogenous rhythms, the environment, and temporal expectancy.

The ability to form temporal expectations of *when* relevant events will occur enables anticipatory coordination with an ever-changing environment. Due to such rapidly changing external dynamics, proactively adjusting one's neurobehavioral state[1] according to predicted demands proves more adaptive than a reactive approach (Schulkin and Sterling 2019): by the time one deploys a reaction, it is often already too late. While timely behavior is less a matter of life or death in the modern world, it is nonetheless crucial for activities like speech comprehension (Corriveau and Goswami 2009; Tierney et al. 2015; Zhao and Kuhl 2016), social interaction (Larson and Zemke 2003), and sensorimotor synchronization (Repp 2005; Repp and Su 2013).

Neural oscillations are commonly espoused as integral to sub-second fluctuations of attentional state (Zalta et al. 2020). Indeed, studies find that perception waxes and wanes with

[1] *Neurobehavioral state* broadly encompasses the state of the brain, body, and mind; as such, this term will be used interchangeably with *arousal state*, *cortical state*, and *attentional state* throughout this text.

oscillatory phase (Mathewson et al. 2009; Neuling et al. 2012); and additional research reports entrainment and phase-resetting of ongoing brain rhythms to external stimulation (Lakatos et al. 2008; Fiebelkorn et al. 2011). Although oscillations above 1 Hz receive significant attention, infraslow oscillations have been found to modulate faster oscillations and may potentially relate to cortical excitability (Monto et al. 2008). Thus, overall arousal and cortical state are underappreciated contributors to fluctuations in attentional state that influence the ability to adaptively interact with one's environment (Khalil et al. 2013; Barbot and Carrasco 2018).

Cholinergic and Noradrenergic Modulation of Cortical State

Cortical states exist along a continuum of varying spontaneous activity and neuronal correlation (Harris and Thiele 2011; Minces et al. 2017; Figure 2.1). At one end, highly synchronous spontaneous fluctuations render neurons largely insensitive to environmental stimuli, as seen in the *up* and *down* states of sleep (Steriade et al. 1993; Volgushev et al. 2006; Curto et al. 2009). At the other end, highly desynchronized cortical activity with reduced interneuronal correlations facilitates a higher signal-to-noise ratio and more faithful encoding of external stimuli (Poulet and Petersen 2008; Minces 2010; Poulet and Crochet 2019). This second state corresponds to active wakefulness, increased arousal, and – at its extreme – hypervigilance (Thiele and Bellgrove 2018).

A multitude of neurochemicals contribute to arousal and cortical state, including monoamines, acetylcholine, glutamate, and GABA, in addition to neuroactive hormones and peptides (Aston-Jones et al. 1994; Sarter and Bruno 1999; Valdez and Koob 2004; Arnsten 2009). However, the preponderance of research on cholinergic and noradrenergic projections to cortex specifically implicates their role in augmenting arousal (Collins et al. 2023).

Acetylcholine release in cortex reduces low-frequency, synchronized activity and decorrelates signal and noise, thus increasing the coding capacity of cortical networks and strengthening stimulus-driven attention (Minces 2010; Záborszky et al. 2018a). In contrast, when cholinergic input is low or pharmacologically inhibited, neuronal activity exhibits synchronous slow waves characteristic of slow-wave sleep (Riekkinen et al. 1991). Nonetheless, effects of cortical cholinergic input on cognitive performance demonstrate an inverted U-shaped curve, in which excessively high acetylcholine activity induces a hypervigilant state with heightened sensitivity to unexpected stimuli (Bentley et al. 2004; Yu and Dayan 2005; Chiba and Krichmar 2020; Mineur and Picciotto 2021). Such a state is adaptive in the context of impending threat but disrupts selective attention and cognitive flexibility (Záborszky et al. 2018b). The primary source of cholinergic projections lies in the basal forebrain: the medial septum, nucleus of the diagonal band, and substantia innominata–nucleus basalis (Alheid and Heimer 1988; Fritz et al. 2019). The basal forebrain, in turn, receives feedback from the cortex alongside inputs from the amygdala, paraventricular nucleus of the hypothalamus, dorsal raphe nuclei, locus coeruleus, and various other regions, which cumulatively may convey environmental salience and behavioral demands relevant to cortical state (Jones and Yang 1985; Baxter and Chiba 1999; Hu et al. 2016).

Norepinephrine from the locus coeruleus modulates cortical state both directly, through noradrenergic projections to cortex, and indirectly, through projections to the basal forebrain (Samuels and Szabadi 2008). Norepinephrine release in the basal forebrain further excites cholinergic cortical projections but has more nuanced effects in cortex. Specifically, norepinephrine strengthens primary sensory cortices, yet – similar to ACh – exhibits an inverted U-shaped curve in its effects on the prefrontal cortex (PFC; Aston-Jones et al. 1994; Arnsten 2015). Norepinephrine release in the PFC enhances working memory and selective attention at moderate levels but demonstrates detrimental effects at both low and high concentrations (Aston-Jones and

Cohen 2005; Arnsten 2009; McEwen and Morrison 2013). The locus coeruleus, like the basal forebrain, receives dense feedback projections from the PFC and afferent input from the amygdala, hypothalamus, and brainstem (Aston-Jones et al. 1994; Sara and Hervé-Minvielle 1995; Samuels and Szabadi 2008).

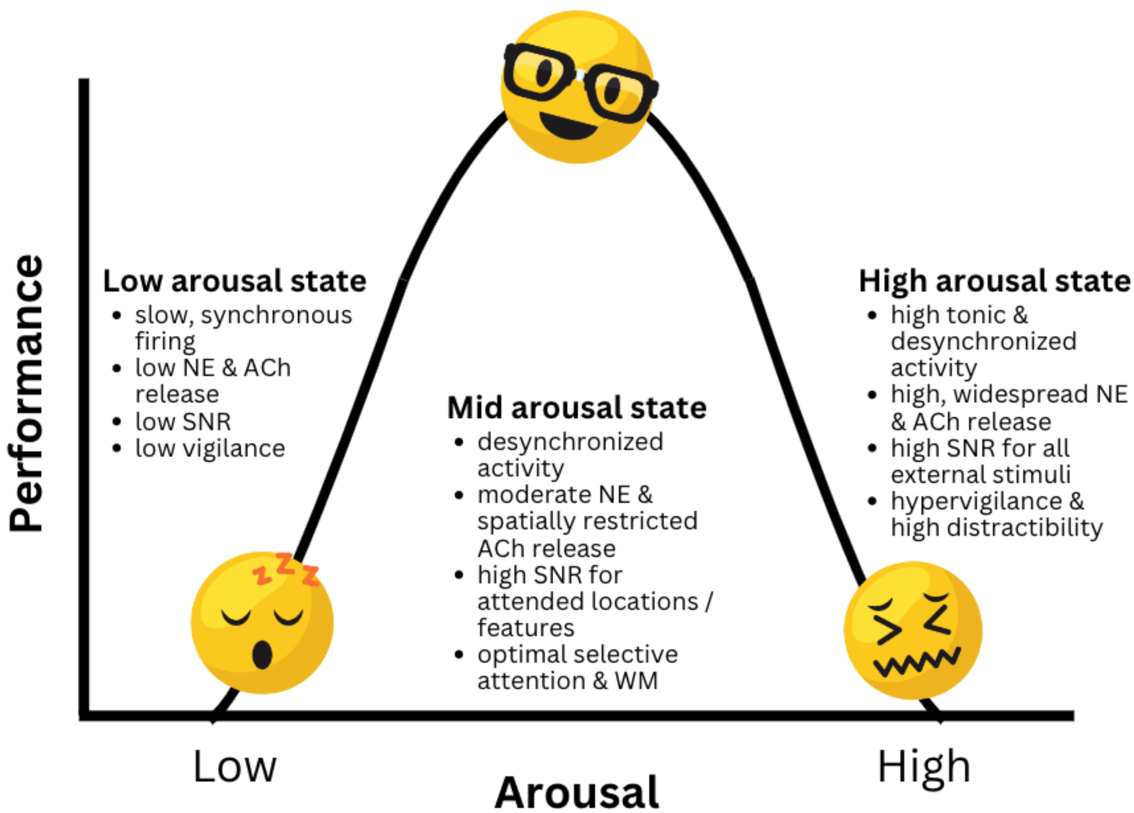

Figure 2.1: The arousal continuum. Neurobehavioral states vary across arousal levels, with moderate arousal most conducive to cognitive performance. The relationship between arousal and performance can be visualized as an inverted U-shaped curve (the "Yerkes-Dodson Law"; Yerkes and Dodson 1908). NE, norepinephrine; ACh, acetylcholine; SNR, signal-to-noise ratio; WM, working memory.

Arousal Fluctuations via an Extended Autonomic System

Inputs to the basal forebrain and locus coeruleus from the amygdala, hypothalamus, and brainstem regions – which partly comprise a central autonomic network (CAN; Benarroch 1993) – suggest that more peripheral signals also modulate cortical state. The CAN refers to a hierarchy of brain regions that influence autonomic nervous system activity, including medial and orbital prefrontal cortex, anterior cingulate, and insula at the cortical level; the amygdala, hippocampus, and hypothalamus at the subcortical level; and various medullary nuclei, the nucleus ambiguus (NA), dorsal motor nucleus of the vagus nerve (DVN), and nucleus of the solitary tract (NTS) in the brainstem (Lamotte et al. 2021; Figure 2.2).

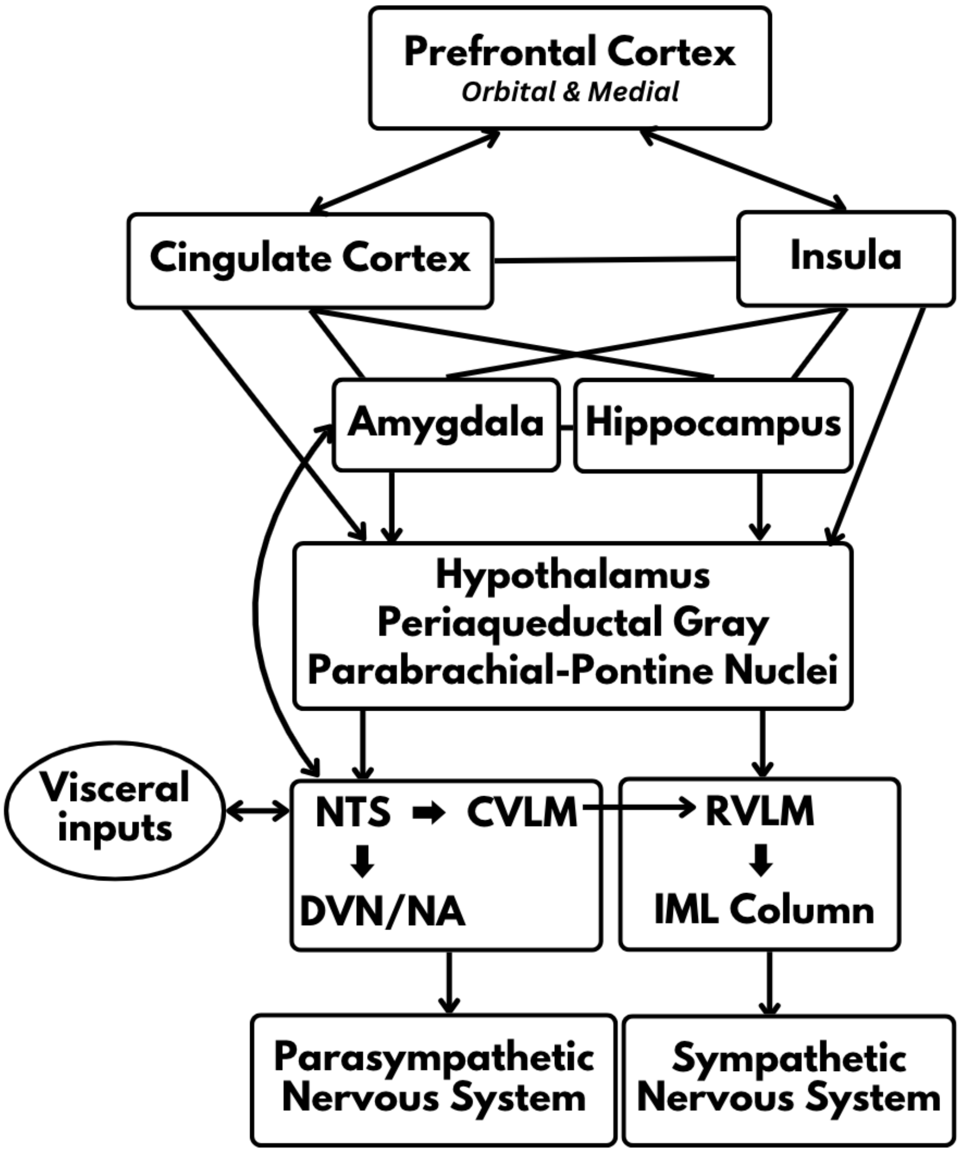

Figure 2.2: Central autonomic network. A simplified diagram of connectivity between brain and body, with the central autonomic network (CAN) at its core. Adapted from Thayer et al. (2009). CVLM, caudal ventrolateral medulla; DVN, dorsal motor nucleus of the vagus nerve; IML, intermediolateral nucleus; NA, nucleus ambiguus; NTS, nucleus of the solitary tract; RVLM, rostral ventrolateral medulla.

Regions of the hypothalamus and brainstem involved in the CAN not only send output to the autonomic nervous system but also receive afferent inputs. In particular, afferent vagal innervation of the NTS allows visceral information and parasympathetic activation to exert widespread effects on the brain – supporting the gut-brain and heart-brain axes. Such bidirectional connections between the CAN and peripheral nervous system allow both the brain to influence and be influenced by the physiological state of the body (Lamotte et al. 2021). The highly integrated nature of the brain and body has received support in Porges' *polyvagal theory* (Porges 2009; Porges and Furman 2011), Thayer's *neurovisceral integration model* (Thayer and Lane 2000), Sterling and Eyer's concept of *allostasis* (Sterling and Eyer 1988), and Goldstein's *extended autonomic system* (Goldstein 2020, 2021).

Cumulatively, all four frameworks emphasize the role of the brain as a mediator and target of the centrally mediated stress response. That is, through the sympathoadrenal medullary axis and hypothalamic-pituitary-adrenal axis, the brain activates the sympathetic nervous system in response to a stressor and initiates a signaling cascade that shifts both physiological and cortical state. In turn, visceral afferent information, such as respiratory and heart rate, feeds into the NTS and other brainstem regions, eventually influencing upstream cortical and subcortical activity (Cechetto 1987). As a result, arousal at the level of the brain and body arise from the same input; and cortical state is coordinated with respect to the relative activity of the sympathetic and parasympathetic branches of the autonomic nervous system.

Deployment of the stress response activates the sympathetic nervous system while simultaneously shifting cortical and subcortical dynamics (McEwen 2013). Specifically, stimulation of the basal forebrain and locus coeruleus induces hypervigilance in sensory cortices and impairs executive functioning in the PFC (Arnsten 2009). At the subcortical level, stress activates regions involved in more reactive behavior, such as the amygdala, striatum, and hypothalamus (Arnsten 2015; Koob and Schulkin 2019). Accordingly, the stressed brain supports optimal detection of environmental threat and immediate action to enable short-term survival (Oken et al. 2006; Table 2.1).

Table 2.1: Multi-level changes supporting high arousal. Increased arousal is mediated by a cascade of neurophysiological changes that ultimately support behaviors favoring immediate survival. *Note: This table includes some, but not all, of these changes.* ACh, acetylcholine; CRF, corticotropin-releasing factor; DA, dopamine; E, epinephrine; GABA, gamma-aminobutyric acid; HPA, hypothalamic-pituitary-adrenal; NE, norepinephrine, NPY, neuropeptide Y.

	Changes during High Arousal	
Observational Level	***Increase***	***Decrease***
Chemical	• ACh • Catecholamines: DA, E, NE • CRF • Cortisol	• GABA • NPY
Neural	• Amygdala • Basal forebrain, locus coeruleus • Striatum • HPA axis • Sympathetic nervous system	• Prefrontal cortex • Hippocampus • Parasympathetic nervous system
Behavioral	• Stimulus-driven attention • Vigilance • Habits • Immediate gratification • "Fight or flight"	• Selective attention • Working memory • Planning • Delayed gratification • Cognitive flexibility

The stress response mediated by sympathetic activation is tamed by the parasympathetic nervous system, which gives rise to a starkly different neurobehavioral state (Porges 1997; Thayer and Lane 2000). In the *relaxed brain*, vagally mediated parasympathetic activation favors neural processing of *internal* over external stimuli. Insensitivity to environmental stimuli, as in the "down" states of deep sleep, reflect this parasympathetic state at its extreme (Luczak et al. 2009; Honey et al. 2017; Ishikawa 2023). However, at more moderate levels observed during wakefulness, this state supports prefrontal mediation of working memory, planning, delayed gratification, and cognitive flexibility; and inhibition of subcortical structures subserving reactive, stimulus-driven, and habitual behaviors (Arnsten 2015; Figure 2.3).

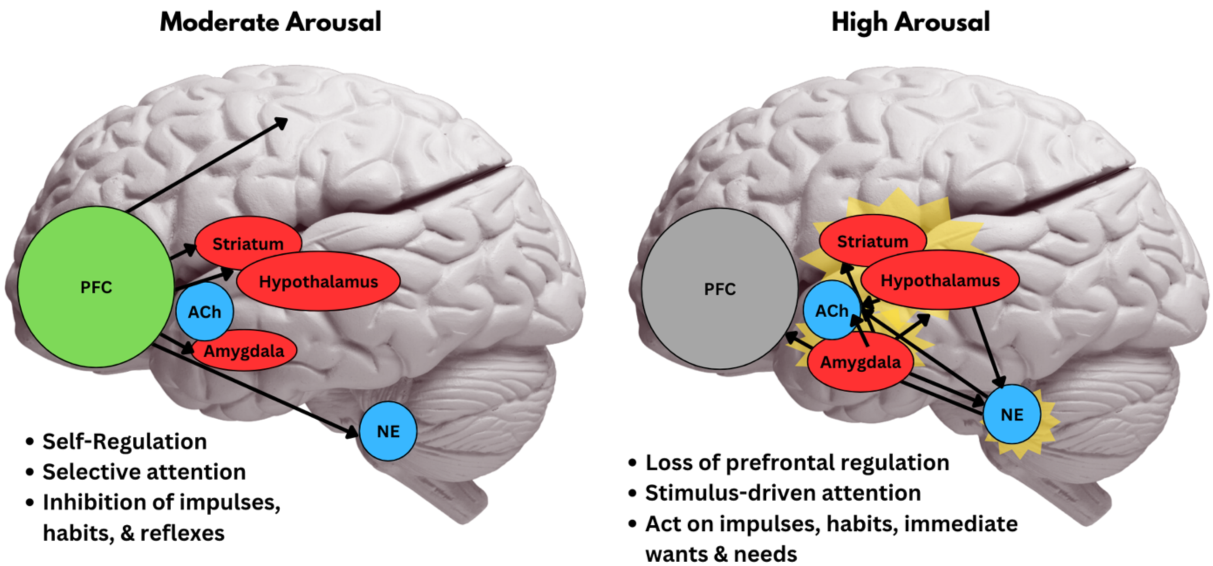

Figure 2.3: Cortical-subcortical balance during moderate and high arousal. During moderate arousal, the prefrontal cortex can provide top-down regulation of subcortical structures to inhibit the stress response and more reactive behaviors. During high arousal, the prefrontal cortex effectively goes "off-line" and subcortical activity dominates, impairing executive functioning while enhancing stimulus-driven attention and impulsive, habitual behaviors serving immediate wants and needs. Adapted from Arnsten (2009).

Simplistically, neurobehavioral states of higher and lower arousal are accompanied by increased sympathetic and parasympathetic activity, respectively. A delicate balance between these two states facilitates optimal attentional state and cognitive performance (Porges 2022). Excessively high arousal leads to stimulus-driven reactive behavior, while excessively low arousal shuts off responsiveness to one's environment. This balance is encapsulated by the Yerkes-Dodson law, yet another inverted U-shaped curve, in which an optimal level of arousal supports optimal performance (Yerkes and Dodson 1908; Rajagovindan and Ding 2011). Nevertheless, specific task demands determine the precise arousal level best suited for performance in any given individual. Consequently, the ability to flexibly shift one's neurobehavioral state to changing task demands proves crucial to adaptive behavior.

Experiential Influences on State Flexibility via Allostasis

The ability to flexibly shift among varying states of arousal derives from the notion of allostasis. Sterling and Eyer first proposed allostasis to explain arousal pathology, providing an alternative to the rigid equilibrium of homeostasis (Sterling and Eyer 1988). In contrast to the static, predetermined set points of homeostasis, allostasis involves more dynamic set points that change according to environmental demands. Moreover, allostasis implicates an interconnected brain-body system, in which the brain integrates peripheral signals to guide system-wide changes. To enable such adaptations, allostasis harnesses feedforward connections in addition to homeostatic negative feedback loops (Schulkin et al. 1994).

Allostatically mediated predictive regulation offers a more timely and energetically efficient approach than homeostasis (McEwen and Wingfield 2003; Singer et al. 2004; Mushiake 2022). In a chronically arousing, demanding, or dangerous environment, adjusting one's baseline to a higher arousal state is more adaptive than continually shifting to and from a homeostatic baseline of lower arousal. Accordingly, chronically high environmental demands lead to chronically high levels of arousal, manifest as a lasting change in autonomic balance with sympathetic dominance. This shift in baseline, or "allostatic state," can be protective in a perpetually unsafe environment but persists even after environmental demands lessen. The latter case reflects maladaptation due to overactivity of feed-forward connections, breakdown of negative feedback, and runaway excitation (Koob and Le Moal 2001; Ullmann et al. 2019).

Autonomic inflexibility accompanying a chronic high-arousal allostatic state arises partly from a breakdown in cortisol negative feedback and from hyperactivity of feed-forward interactions between the amygdala and locus coeruleus (Van Bockstaele et al. 1996; Curtis et al. 2002; Shekhar et al. 2005). In particular, cortisol levels remain elevated due to compensatory receptor downregulation or desensitization, as well as from atrophy of hippocampal and prefrontal sites that provide negative feedback to the HPA axis. In turn, cortisol increases synthesis of corticotropin-releasing factor in the amygdala, which stimulates the locus coeruleus to release norepinephrine back onto the amygdala, resulting in further CRF release. In combination with weakened negative feedback, this CRF-NE-CRF system causes a self-perpetuating cycle that further activates brain regions mediating the stress response (for review, see Ross and Van Bockstaele 2021). As a result, entering states of lower arousal becomes increasingly improbable.

Cumulatively, these allostatic adaptations impede arousal fluctuations across all time scales. Daily cortisol rhythms flatten and the frequency of ultradian cortisol pulses increases, both of which may contribute to sleep disruptions (Hirotsu et al. 2015). Finer-scale fluctuations of dynamic attention are replaced by a more constant state of attentiveness – or hypervigilance – that casts a wide spatial attentional net to detect potential threats at any time and location. The capacity to match one's internal state with environmental dynamics goes awry, and what was initially an adaptive response becomes a liability (Agorastos and Chrousos 2022).

Sources of Arousal: A Broad Definition of Stress

Experience of high environmental demands and a corresponding high-arousal allostatic state can be considered a form of stress. Within the brain and body, the terms *arousal* and *stress* typically refer to the same process: arousing stimuli inherently activate the stress response and thus can be considered stressors. Furthermore, although the majority of research on the stress response employs paradigms that elicit psychological stress, the definition of stress expands far beyond subjective perception. Rather, stress refers to *any* stimulus or experience that perturbs physiological or psychological homeostasis (Sapolsky 2004). As such, stress is experienced as much in the body as it is in the mind; and many of our daily behaviors, from physical activity to diet, can affect allostatic load (Schulkin et al. 1994; Grupe and Nitschke 2013; Park et al. 2020).

It is important to distinguish between stressors that contribute to allostatic load and those that enhance resiliency (Karatsoreos and McEwen 2011; Chbeir and Carrión 2023). The former, comparable to distress, can be differentiated from the latter, or eustress, in their severity and time course. Eustress is typically an acute, tolerable – or even enjoyable – challenge to which one can effectively and favorably adapt (Selye 1956). For instance, appropriately programmed exercise can improve cardiovascular endurance or strength conditioning (Eöry et al. 2021; Adams-Campbell et al. 2022). In contrast, distress includes excessively intense, traumatic, or chronic stressors, which ultimately impede recovery capacity, induce chronic arousal, and augment allostatic load.

In addition, because stress is primarily indifferent to valence, excessive reward can also be considered a stressor. As is the case of addiction, continual activation of the reward system leads to reward dysregulation and arousal pathology. Accordingly, both *too much of a bad thing* and *too much of a good thing* can activate similar allostatic mechanisms to induce maladaptation and autonomic inflexibility (Slavich 2020).

Role of Prefrontal Cortex in Allostasis and Autonomic Flexibility

Though the medial prefrontal cortex (mPFC) consists of subdivisions that subserve varied functions depending on their connectivity, this region as a whole plays a vital role in autonomic flexibility through its context-dependent modulation of autonomic balance (McKlveen et al. 2015; Kim 2020). For instance, research indicates that the mPFC enables extinction of fear conditioning, cognitive reappraisal of emotion, and anticipatory autonomic responses when contemplating risky decisions (Bechara et al. 1999; Phelps et al. 2004; Izuma et al. 2015). As the most evolutionarily recent component of the CAN, the mPFC lies in a prime position to integrate external and internal signals in aims of adaptively modulating one's behavior and state (Barbas and Zikopoulos 2007; Hänsel and von Känel 2008). Individuals with mPFC damage demonstrate deficits in a wide range of self-regulatory processes, such as behavioral inhibition, delayed gratification, planning, and autonomic reactivity (Van Eden and Buijs 2000). These deficits are similar to those seen in states of chronically high arousal.

The role of the mPFC in autonomic flexibility and self-regulation underlies its contribution to social interactions, as social engagement requires one to coordinate their internal state with that of others (Franklin et al. 2017). In fact, some suggest that autonomic flexibility developed primarily for the purpose of social engagement. Disorders involving impaired social behavior, like autism (Gilbert et al. 2008; Shalom 2009) and ADHD (Vidor et al. 2022), implicate the mPFC; and mPFC damage alone may replicate autistic personality traits (Umeda et al. 2010). Perhaps the famous case of Phineas Gage best exemplifies the gross disruption in sociality arising from mPFC damage: after his injury, he was described as "fitful, irreverent…manifesting but little deference for his fellows, impatient…His mind was radically changed, so decidedly that his friends and acquaintances said he was 'no longer Gage'" (Harlow 1993).

Nevertheless, similar symptoms – albeit milder – can occur without overt mPFC damage, via arousal pathology and allostasis. During acute states of high arousal, excessive norepinephrine and dopamine release trigger receptor signaling cascades that inhibit mPFC activity. In chronic high-arousal allostatic states, dendritic retraction in medial prefrontal neurons further weakens the modulatory influence of the mPFC on the stress response, leading to a concomitant increase in subcortical activity underlying sympathetic dominance, autonomic inflexibility, and reactive behavior (Arnsten 2009).

Allostatic State in Brain and Behavior: When Adaptation Goes Awry

As one remains in a chronic high-arousal state, it becomes progressively harder to return to a lower arousal baseline. At the neural level, breakdown of negative feedback alongside overactive feedforward connections elicits adaptations that weaken the PFC while strengthening the amygdala and subcortical structures. These allostatic changes lead to shifts in neurobehavioral state that reinforce the self-perpetuating cycle of arousal pathology, whereby high-arousal states spur behaviors that further elevate arousal.

A hypervigilant attentional state, mediated by noradrenergic and cholinergic projections to cortex, heightens sensitivity to unexpected and perceptually salient stimuli. Though adaptive in a truly dangerous environment, hypervigilance becomes a handicap in modern society. At the very least, such sensitivity impedes selective attention, manifesting as distractibility. At worst, it encourages the negative encoding bias common to conditions like depression (Mineur and Picciotto 2021), creating the illusion of an unsafe environment despite lack of overt threat. Consequently, one tends to superfluously deploy the stress response to novel events or stressors, however small.

Arousal pathology further intervenes at the behavioral level with widespread impairments in self-regulation and executive functioning that also exacerbate this allostatic state. For instance, socially disinhibited or anxious behavior may lead to aggression or avoidance, respectively, and, as a result, degrade interpersonal interactions. Impairment in delayed gratification coupled with cravings for salty, highly palatable, and calorie-dense foods may spawn poor dietary choices and overeating. Additionally, alterations in reward thresholds require greater amounts of rewards for the same gratification. Impulsivity and reward system dysfunction predispose addiction in its many forms: to drugs and gambling as well as to food and social media. Each of these behavioral changes increases exposure to perceived stress – as in the case of poor social connection – or excessive reward – as with junk food or drugs – thereby augmenting arousal levels.

Thus, conditions of chronic high arousal induce neural changes that alter attention and behavior, leading to enhanced stress reactivity, behavioral disinhibition, and addictive tendencies. This pervasive prioritization of short-term satisfaction or perceived safety over long-term health proceeds to increase arousal and exacerbates neurophysiological (mal)adaptations. Over time, these cumulative changes exert a "wear and tear" on the brain and body, or *allostatic load*.

The Impact of Lifestyle Choices on Allostatic Load

On the one hand, chronic high-arousal states motivate shortsighted decisions and health risk behaviors; on the other hand, these same behaviors exacerbate arousal and allostatic load. Unfortunately, such behaviors have become particularly common in modern society due to widespread availability of arousing and rewarding stimuli. For example, technological advances have spawned laptops and smartphones, which provide nearly immediate reward with the tap of a finger. The development of processed and fast food offers easily accessible, highly palatable fare. Meanwhile, the rise of office jobs, video games, and streaming services encourages sedentary lifestyles with lower energy expenditure – so high-calorie meals are more likely to elicit weight gain, causing additional physiological stress. Screens and household lighting make it far too easy to pull a late night or occasional all-nighter; and socioeconomic pressures generate psychogenic stress, especially in lower income communities. These varied arousing stimuli and stressors all converge on the same brain-body system, activating the stress response and augmenting allostatic load. So, while today's environment arose from technological and industrial advancements enabled by human ingenuity (and the PFC), it is this very environment that degrades prefrontal processes and overall health.

Technology

Digital media usage has progressively increased in recent years, with teenagers in the United States averaging over seven hours a day in screen time (Rideout and Robb 2019). The COVID-19 pandemic has further increased the use of technology for education, communication, and entertainment (Nielsen 2020). While digital media provides diverse opportunities and broad access to varied information, its mis- or over-application may contribute to arousal pathology and allostatic load.

Digital media may indirectly stimulate arousal and stress through its effects on sleep, dietary choices, and physical activity. For instance, greater use of social media – especially late in the night – has been found to disrupt sleep, resulting in more frequent awakenings and poorer sleep quality (Christensen et al. 2016; Levenson et al. 2016, 2017; Cabré-Riera et al. 2019; Lee et al. 2023). Given sleep deprivation is a well-known stressor (McEwen 2006; McEwen and Karatsoreos 2015) associated with negative mental health outcomes (Alonzo et al. 2021), these effects may partially mediate the relationship between social media usage and poor mental health. Furthermore, daily technology use is linked to unhealthy food choices (Cox et al. 2012; Lwin et al. 2017), physical inactivity (Serrano-Sanchez et al. 2011; Fan et al. 2022), and obesity (Arora et al. 2013; Bickham et al. 2013), which create allostatic load by degrading physiological health.

Excessive screen time may more directly elevate arousal by encouraging multitasking and constantly engaging stimulus-driven attention. In particular, technology feeds the propensity to multitask (Aagaard 2015; van der Schuur et al. 2015) – or, rather, to rapidly task switch. In the case of texting while driving, such “multitasking” becomes dangerous (Ige et al. 2016); but even more innocuous forms of multitasking can elicit a physiological response similar to that evoked by a perceived stressor (Becker et al. 2023). In addition, continually disengaging from the “real world” to tend to virtual affairs removes one from the present moment and reinforces a state of distractibility. Along these lines, social media further strengthens distractibility by offering a continuous, ever-changing stream of salient stimuli, which spurs rapid shifts of stimulus-driven attention and induces high arousal (Pengnate 2016; Jennings and Tabatabaeian 2023). Perhaps not surprisingly, greater screen time correlates with symptoms of ADHD (Nikkelen et al. 2014). While such correlational research cannot determine the directionality of causality, given the mutually reinforcing nature of allostatic adaptations, it is likely that attentional deficits both predispose and are worsened by excessive digital media usage.

Though the effects of social media are somewhat controversial, they include both benefits and drawbacks. Regarding the former, social media enables the formation of long-distance connections and exposure to diverse perspectives, cultures, and ways of life. Moreover, online groups allow one to connect with like-minded individuals holding common values and goals. These virtual but nonetheless meaningful interactions have been associated with measures of wellbeing (Seabrook et al. 2016; Verduyn et al. 2017). However, when asynchronous communication on social media is used to replace real-time interactions, it may lead to unfavorable outcomes. In which case, excessive screen time has, ironically, been associated with social isolation (Martin 2011; Primack et al. 2017; Meshi and Ellithorpe 2021) and impaired recognition of nonverbal communication (Kirsh and Mounts 2007; Uhls et al. 2014).

Adolescents are particularly attracted to and affected by digital media due to their developing brains. Their immature PFC makes them particularly susceptible to the immediate reward provided on social media and in internet games (Giedd 2012). In fact, the internet may, in many ways, cater to adolescent hunger for social connection, adventure, and information (Giedd 2020). These desires, coupled with the highly reinforcing structure of online games, render the adolescent brain prone to addiction. Accordingly, the DSM-5 has recently introduced *internet gaming disorder* to recognize the preoccupation with, tolerance to, and withdrawal from gaming that has become increasingly problematic (American Psychiatric Association 2022). With the COVID-19 pandemic has come a greater prevalence of addictive social media use, likely due to heightened stress levels that predispose such addictive behavior (Zhao and Zhou 2021). In turn, addiction itself has been explained as arousal pathology and thus reinforces chronic stress (Koob and Le Moal 2001).

Diet

Advancements in food processing have enabled a steady and safe food supply, eliminating the most common pre-industrial stressor: famine. In fact, today's food environment features a plethora of convenient, flavorful food products that can be purchased in stores, ordered at restaurants, or delivered at home. While the threat of starvation has abated with these developments, a rise in obesity (Malik et al. 2013), diabetes (Gregg et al. 2014), and heart disease (Roth et al. 2020) has taken its place. The so-called "Western diet" of highly palatable, packaged foods rich in fat and sugar is associated with a variety of chronic ailments and markers of allostatic load (Mattei et al. 2011; Clemente-Suárez et al. 2023). The Western diet likely contributes to such physiological stress by spurring over-eating and weight gain; by allostatically upregulating the stress response; by disrupting the gut microbiome; and by reducing micronutrient intake.

The high palatability of ultra-processed foods common to the Western diet renders them highly rewarding – so much so that they can override satiety signals to induce overeating (Small and DiFeliceantonio 2019). Overconsumption of these low-quality, high-calorie foods over time can lead to weight gain, obesity, and metabolic syndrome (Askari et al. 2020; Frías et al. 2023; Mambrini et al. 2023). Furthermore, diet and psychogenic stress interact, with stress spurring cravings for calorie-dense "comfort" foods, the consumption of which appears to dampen the stress response (Dallman et al. 2003; Rabasa and Dickson 2016). Consumption of highly palatable foods high in sugar and/or fat has been found to reduce levels of stress-signaling compounds, including adrenocorticotropic hormone (ACTH; Zeeni et al. 2015), CRF (Warne 2009), and glucocorticoids (Di Polito et al. 2023). Interestingly, research suggests a synergism between diet and psychogenic stress, in which consumption of calorie-dense foods may lead to greater metabolic dysregulation specifically when stressed (Aschbacher et al. 2014). Thus, high-calorie processed foods are apt to drive overeating in both stressed and non-stressed individuals, with the former particularly predisposed to binging and its adverse consequences.

By increasing cardiometabolic stress, overeating and subsequent weight gain contribute to allostatic load. The systemic toll of excessive fat gain in overweight and obesity increases the risk of various diseases, such as diabetes, cardiovascular disease, and osteoarthritis (Lim and Boster 2023). Moreover, obesity shares a bidirectional relationship with brain and cognitive functioning: impaired prefrontal inhibition and mesocorticolimbic dysregulation increases the risk of obesity, and obesity weakens the prefrontal cortex and self-regulation (Lowe et al. 2019). These neural alterations are seen both functionally in fMRI activation (Batterink et al. 2010; Kishinevsky et al. 2012) and structurally as prefrontal reductions in gray and white matter (Kullmann et al. 2015; Willette and Kapogiannis 2015).

In addition to encouraging overeating and obesity, highly processed foods provide a sufficiently potent reward to directly induce addiction and arousal pathology (Parylak et al. 2011). Similar to drug addiction, hyperpalatable food provides both positive and negative reinforcement by eliciting pleasure and acutely taming the stress response; repeated consumption of these palatable foods recruits allostatic mechanisms that upregulate stress circuitry while dysregulating reward pathways. Animal models of food addiction demonstrate symptoms akin to those observed with drug addiction, such as tolerance to (Colantuoni et al. 2001; Bello et al. 2009), dependence on (Colantuoni et al. 2002), and withdrawal from (Parnarouskis et al. 2022) palatable food.

The gut microbiome offers another means by which diet can exert widespread effects on the brain and body. The vagus nerve alongside gut microbiota production of short-chain fatty acids (SCFAs; Silva et al. 2020), cytokines (Agirman et al. 2021), and neurotransmitters (Strandwitz 2018) provide numerous routes of communication between the gut, brain, and body. Cytokines, in particular, provide a manner through which gut dysbiosis and inflammation can stimulate the stress response, as interleukin (IL)-1 and IL-6 have been found to activate the HPA axis via actions at the hypothalamus (Späth-Schwalbe et al. 1994; Goshen and Yirmiya 2009). An excess of dietary fat, as is common in the Western diet, has been found to reduce gut microbial diversity; and high saturated fat, specifically, increases levels of certain microbes that may be related to the development of obesity and pro-inflammatory disease (Wan et al. 2019; Wolters et al. 2019; Bailén et al. 2020). Similarly, consumption of a low-fiber diet reduces microbial diversity, reducing production of anti-inflammatory SCFAs and increasing prevalence of microbes that feed on the intestinal mucosal lining (Sonnenburg and Sonnenburg 2019). Additionally, various additives found in processed foods affect the gut microbiome and have the potential to induce dysbiosis (Cao et al. 2020; Raoul et al. 2022).

The poor micronutrient content of the Western diet may also adversely affect the gut microbiome (Hibberd et al. 2017) and compromise numerous physiological processes critical to basic functioning and overall health (Bailey et al. 2015). Most micronutrient-dense foods – such as fruits, vegetables, nuts, seeds, seafood, and minimally processed meats – are relatively lacking in the Western diet, which primarily leans on highly processed, refined foods devoid of most vitamins and minerals (Cordain et al. 2005). In fact, the 2015-2020 Dietary Guidelines for Americans reported gross underconsumption of vitamin D, calcium, potassium, iron, choline, magnesium, and vitamins A, C, and E (U.S. Department of Health and Human Services and U.S. Department of Agriculture 2015). Micronutrient deficiencies arising from these suboptimal dietary patterns can cause physiological stress and impair recovery; and chronic stress depletes many of these same micronutrients, further exacerbating allostatic load (Wishart 2017; Lopresti 2020).

Physical Activity

The modern lifestyle, with its sedentary occupations and leisure activities, has led to a progressive decrease in physical activity levels. Cars are used in lieu of walking; desk jobs have replaced most manual labor; and video games are more popular than playing outside. Unlike ancestral humans, modern day man need not forage or hunt for food, but instead can conveniently buy fast food at a drive-thru. Adults in the United States report an average of 9.5 hours of sedentary time daily (Matthews et al. 2021), and approximately only 25% meet the Physical Activity Guidelines for Americans (Elgaddal et al. 2022). So, while the convenience of the developed world is often considered beneficial, it has spurred some far less favorable reductions in activity. Such sedentary behavior and physical inactivity are associated with a higher allostatic load index (Bu and Li 2023), obesity, hypertension, hypercholesterolemia, metabolic syndrome, type 2 diabetes, cardiovascular disease, and all-cause mortality (de Rezende et al. 2014).

Sedentary behavior contributes to physiological stress by spurring metabolic dysregulation and inflammation, which is intensified in the case of weight gain and obesity. Physical inactivity – independent of weight gain – contributes to insulin resistance (Hamburg et al. 2007; Yaribeygi et al. 2021), mitochondrial dysregulation (Figueiredo et al. 2009; Distefano et al. 2018), oxidative stress (Laufs et al. 2005; Kozakiewicz et al. 2019), and systemic inflammation (Højbjerre et al.

2011; Hamer et al. 2012; Phillips et al. 2017). When combined with overeating, lower energy expenditure from physical inactivity can lead to visceral fat accumulation and obesity (Laye et al. 2007; Pietiläinen et al. 2008; Belavý et al. 2014), both of which exacerbate these same pathologies and add further cardiometabolic stress (Valenzuela et al. 2023).

Greater activity of the sympathetic nervous system also accompanies a sedentary lifestyle, with allostatic adaptations seen in both in brain and body. For instance, peripheral changes in hypertension and cardiovascular health may, at least partially, be mediated by changes in the rostral ventrolateral medulla (RVLM), a key brainstem region controlling sympathetic output (Mischel and Mueller 2011; Mischel et al. 2015). Sedentary behavior has been found to increase the sensitivity and recruitment of neurons in this region, enhancing excitatory inputs while decreasing inhibitory inputs (Mueller and Mischel 2012; Mischel et al. 2014; Subramanian et al. 2014; Mueller et al. 2020); these adaptations cumulatively cause greater sympathetic tone and reactivity. Furthermore, physical inactivity is associated with lower gray matter volume in the hippocampus and PFC (Erickson et al. 2014), both of which play a crucial role in inhibiting the stress response. The "adaptive capacity model" (ACM) posits these changes to reflect adaptive capacity reductions that minimize energy expenditure in absence of physical activity (Raichlen and Alexander 2017). According to the ACM, physical activity and brain health are intrinsically coupled due to human evolutionary history, in which effective foraging behavior simultaneously utilized both motor and cognitive processes. Consequently, chronic physical inactivity encourages atrophy of areas involved in cognitively demanding tasks and accompanying impairments in executive functioning.

While physical inactivity augments overall stress through these various neurophysiological changes, psychological stress may also impede efforts to be physically active (Stults-Kolehmainen and Sinha 2014). Thus, yet another reciprocal relationship may exist between physical inactivity and chronic stress, reinforcing the pernicious cycle in which long-term activation of the stress response spurs unhealthy behaviors that generate further stress to keep the stress response constitutively active.

Sleep

The integration of artificial lighting and electronic devices into nearly every modern household has offered convenience at the expense of the human circadian rhythm. Personal computers and laptops allow one to work at home, any hour of the day (or night); bedroom televisions provide evening entertainment; and smartphones support late-night scrolling on social media. These seemingly innocuous activities, amongst others, have encouraged circadian rhythm disruption, short sleep duration, and poor sleep quality. Approximately one-third of Americans get insufficient sleep, with an estimated 50-70 million suffering from chronic sleep disorders (National Heart, Lung, and Blood Institute 2022). Consequences of such widespread sleep disturbances include not only fatigue, but also systemic changes in the body and brain that reflect higher allostatic load (McEwen 2006; McEwen and Karatsoreos 2015; Christensen et al. 2022) and correlate with greater risk of cardiovascular disease, diabetes, depression, and obesity (Stein et al. 2008; Norton et al. 2018).

Insufficient sleep may contribute to these detrimental consequences, in part, through effects on diet and physical activity. For instance, poor sleep has been found to augment appetite, presumably due to increased levels of ghrelin – a hunger-inducing hormone – and decreased leptin, a satiety-promoting hormone (Spiegel et al. 2004). Moreover, sleep deprivation impairs self-regulation, which may increase the likelihood of succumbing to food-related temptations and overeating (Dorrian et al. 2019). Reductions in physical activity and energy expenditure often accompany poor sleep as well (Schmid et al. 2009; Benedict et al. 2011; DePorter et al. 2017), predisposing a calorie surplus and associated weight gain.

Inadequate sleep may additionally contribute to allostatic load by increasing sympathetic activity and reducing parasympathetic tone (Zhong et al. 2005; Greenlund and Carter 2022). The parasympathetic nervous system helps support recuperative processes occurring during sleep; and when sleep is disrupted, greater sympathetic activation is likely to ensue, leading to enhanced noradrenergic tone (Irwin et al. 1999; Kim et al. 2013) and an altered cortisol rhythm characterized by higher-than-normal levels of evening cortisol (Leproult et al. 1997; Spiegel et al. 1999). This shift in sympatho-vagal balance may explain the increased blood pressure (Palagini et al. 2013), lower heart-rate variability (Zhong et al. 2005), and impaired insulin sensitivity (Sondrup et al. 2022) often accompanying poor sleep.

The effects of poor sleep extend to the brain, affecting both cortical and subcortical areas to shift the proportionality of brain function. Rodent research demonstrates atrophy of mPFC (Noorafshan et al. 2017) and reduced hippocampal neurogenesis and long-term potentiation (Kim et al. 2005; Fernandes et al. 2015) following sleep deprivation. Human studies report impaired prefrontal modulation of subcortical reward regions and the amygdala, both of which show heightened activation under sleep loss (Yoo et al. 2007; Krause et al. 2017). This shift in brain function favoring more reflexive and reactive networks not only impedes inhibitory control, cognition, and memory, but also increases stress reactivity and impulsivity.

Nevertheless, sleep and stress interact bidirectionally, as poor sleep can both cause and be caused by chronic perceived stress (Hirotsu et al. 2015; Lo Martire et al. 2020). Chronic stress may interfere with sleep both directly, by reducing non-REM sleep, and indirectly, by dysregulating the diurnal cortisol rhythm and elevating evening cortisol (Papale et al. 2005; Lo Martire et al. 2020).

Perceived Stress

The past few years have been tumultuous for many Americans: political divisiveness, the economic downturn, racial turmoil, foreign relations, and the COVID-19 pandemic were all stressors that have taken a toll on mental health. Chronic stress has reached startlingly high proportions, with nearly 7 in 10 Americans reporting increased stress over the course of the pandemic (American Psychological Association 2020). Anxiety disorders affect nearly 40 million adults in the United States (Anxiety & Depression Association of America 2024), and approximately 50% of young adults aged 18-24 report symptoms of anxiety and/or depression (Panchal et al. 2023). The American Psychological Association has referred to this trend as a *national mental health crisis* (American Psychological Association 2020). So, although predation, starvation, and drought no longer plague the developed world, psychological stressors have taken their place. In fact, the burden of these newer chronic stressors originally inspired the model of allostasis – as Sterling and Eyer aimed to explain the rise of chronic disease in modern society (Sterling and Eyer 1988).

While psychological stress is, most overtly, a feeling, it involves a variety of physiological changes that can engender disease in the long-term. Extensive research on chronic psychological stress demonstrates a shift toward sympathetic dominance, with long-lasting dysregulation of the HPA axis (Lucini et al. 2005; McEwen 2005, 2017). Chronic stress is often associated with higher levels of cortisol, norepinephrine, and CRF (Bremner et al. 1997) in human subjects at baseline and/or in response to acute stress; and both animal and human models indicate a shift in brain networks, with functional and structural adaptations favoring amygdala activity while weakening the PFC and hippocampus (Arnsten 2009, 2015; McEwen 2017). These widespread changes increase the risk of both mental and physical illness, predisposing hypertension (Sparrenberger et al. 2009; Liu et al. 2017), cardiovascular disease (Kamarck et al. 2012), anxiety disorders (Charney et al. 1993; Pêgo et al. 2010), and even premature death (Robinson et al. 2004).

Though the amygdala is traditionally credited with regulation of anxiety, fear, and stress, the conscious experience of such emotions requires interactions with higher-order components of the central autonomic network that support emotional appraisal (Barrett et al. 2007). In particular, the mPFC, anterior cingulate cortex (ACC), and insula are strongly implicated in perceived stress and anxiety (Ulrich-Lai and Herman 2009; Cechetto 2014; McKlveen et al. 2015). Connections between these regions and the amygdala – as well as downstream regions like the hypothalamus, nucleus of the solitary tract, and rostral ventrolateral medulla – enable perceived stress to activate the HPA and sympathoadrenal medullary axes to induce peripheral changes (Benarroch 1993). Accordingly, activity of the mPFC, ACC, and insula correlates with changes in blood pressure and heart rate in response to stress (Critchley et al. 2003; Gianaros et al. 2005, 2007, 2011; Wong et al. 2007; Wager et al. 2009).

Given the predictive nature of the brain and body, the majority of perceived stress occurs not in response to a present stressor but in response to an *anticipated* stressor. This anticipatory stress is presumably evoked by a perceived uncertainty surrounding *whether*, *when*, and *what* type of a stressor may occur (Grupe and Nitschke 2013; Peters et al. 2017). As such, predictability of an impending stressor can sometimes ameliorate its negative effects (Seligman et al. 1971); and individual differences in intolerance to uncertainty can influence vulnerability to perceived stress (Demirtas and Yildiz 2019), anxiety (Osmanağaoğlu et al. 2018), and post-traumatic stress disorder (Raines et al. 2019). Environmental dynamics with high uncertainty – whether due to low socioeconomic status, political upheavals, or the pandemic – typically breed stress and anxiety that is most pronounced in individuals with greater intolerance to uncertainty.

Anticipatory activation of the stress response aims to reduce uncertainty by spurring attention, acquisition of information, and learning. In modern society, a convenient means by which many seek to reduce uncertainty resides in the internet. However, although web searches may provide relief to some, they can exacerbate anxiety in others: searching for medical information online can augment health anxiety, a condition termed *cyberchondria* (Starcevic and Berle 2013). Consequently, a behavior that was initially driven to reduce stress ironically increases it.

Chronic perceived stress can also drive health risk behaviors, which serve as temporary coping mechanisms but – similar to googling – can ultimately reinforce stress. For example, chronic stress can stoke appetite and cravings for calorie-dense foods, leading to overeating (Dallman et al. 2003); disrupt sleep quantity and quality (Lo Martire et al. 2020); encourage physical inactivity (Stults-Kolehmainen and Sinha 2014); and predispose addiction to drugs (Sinha 2001), technology (Zhao and Zhou 2021; Qiu et al. 2023), and food (Sinha and Jastreboff 2013). Each stress-induced behavior may provide short-term stress relief that contributes to allostatic load in the long-term, supporting a self-perpetuating stress spiral.

Thus, these diverse lifestyle factors – misuse of technology, poor diet, physical inactivity, insufficient sleep, and chronic perceived stress – all converge on the same stress response, leading to lasting allostatic adaptations in the brain and body that erode both mental and physical wellbeing (see Table 2.2 for a summary). Modern advancements have ushered in a lifestyle of convenience that lacks overt threats to survival seen in less developed societies, but stress has not been eliminated: it has simply taken a different form. The more ancient and acute stressors of famine, drought, and predation have been replaced by more subtle, chronic stressors. These modern stressors include not only adverse experiences, but also "too much of a good thing." Excessive use of technology and overconsumption of hyperpalatable food contribute to allostatic load just as do physical inactivity, poor sleep, and perceived stress.

Moreover, the interconnectedness of these health risk behaviors leads to mutually reinforcing relationships, whereby engagement in one encourages engagement in the others. These interactions mimic those seen at the neural level, in which feedforward connections continually strengthen subcortical stress-related regions and weaken self-regulatory structures, continually stoking the stress response (Figure 2.4). Modern developments have forged an environment that so seamlessly enables continuation of health risk behaviors and chronic stress, further supporting the synergy of these interactive cycles in the brain, body, and behavior. So, although the human brain, with the more "evolved" PFC, has made possible the advancements of modern society, these same advancements have led to a lifestyle and environment that weakens the PFC and higher-order cognitive processes.

Table 2.2: Contributions of lifestyle factors to stress and allostatic load. Excessive technology use, poor diet, physical inactivity, insufficient sleep, and chronic perceived stress contribute to allostatic load through both direct and indirect mechanisms. HPA, hypothalamic-pituitary-adrenal; mPFC, medial prefrontal cortex; PFC, prefrontal cortex; RVLM, rostral ventrolateral medulla.

Lifestyle Factor	***Contributions to Stress & Allostatic Load***
Excessive Technology Use	• Multi-tasking • Stimulus-driven attention • Reduced real-time social interactions • Highly reinforcing "rewards" on social media & virtual games • Encourages unhealthy diet, poor sleep, physical inactivity
Poor Diet	• Ultra-processed foods potently activate brain "reward" pathways • Overeating, fat gain, & obesity • Gut dysbiosis & inflammation • Micronutrient deficiencies
Physical Inactivity	• Metabolic dysregulation & inflammation • Visceral fat accumulation & obesity • Increased sympathetic output from RVLM • Reduced gray matter in hippocampus & PFC
Insufficient Sleep	• Increased sympathetic tone • Flattened cortisol rhythm • Atrophy of mPFC • Reduced hippocampal neurogenesis • Amygdala & subcortical activity • Poor self-regulation • Encourages overeating, poor diet, & physical inactivity
Chronic Perceived Stress	• Sympathetic activation • Long-lasting HPA axis dysregulation • Weakening of PFC & hippocampus • Encourages poor sleep & diet, physical inactivity, excessive technology use

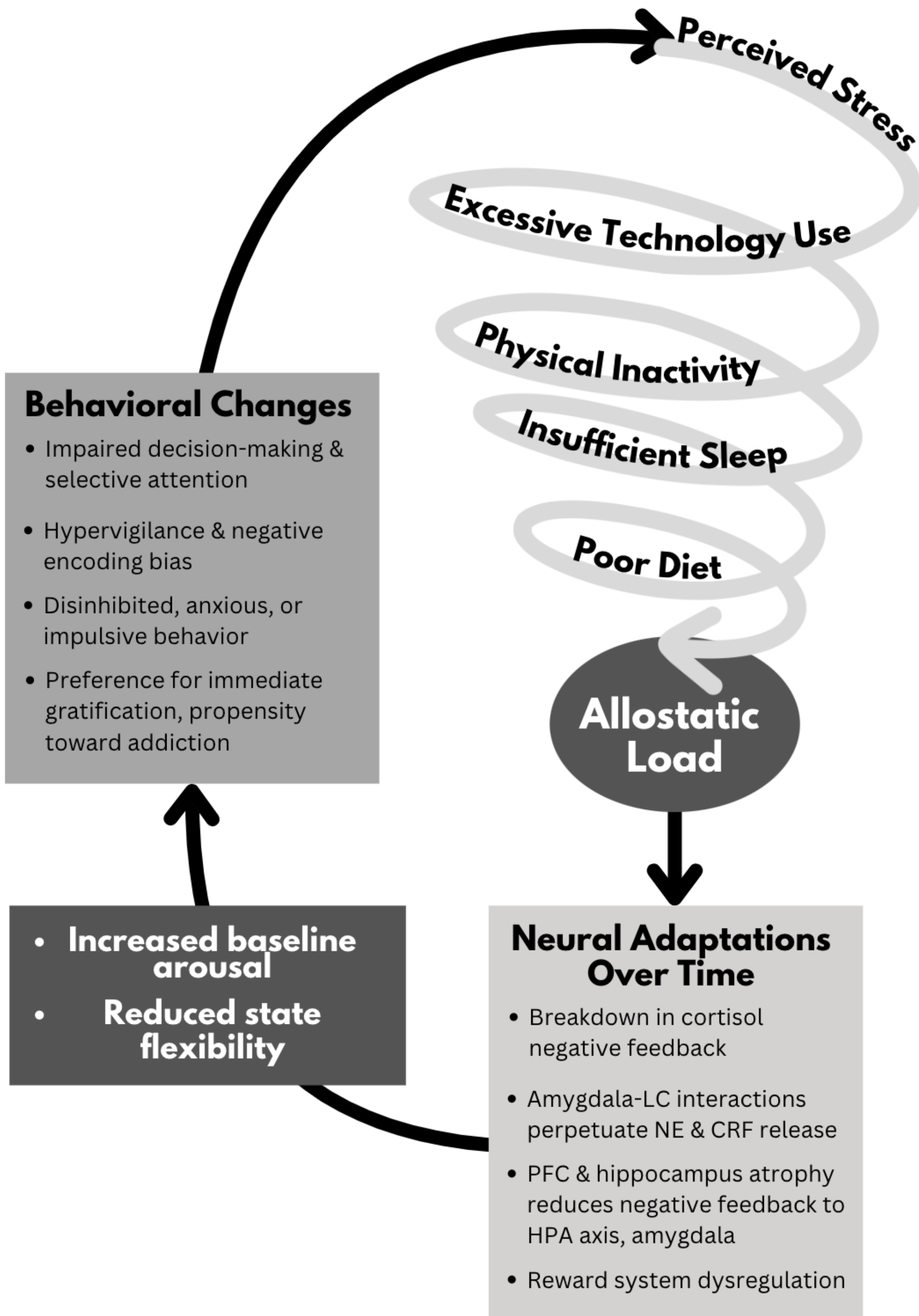

Figure 2.4: The mutually reinforcing cycle(s) perpetuating allostatic load. Perceived stress, excessive technology use, physical inactivity, insufficient sleep, and poor diet cumulatively contribute to allostatic load. Reciprocal relationships between each lifestyle factor, in which engagement in one encourages engagement in the others, creates a "stress spiral" that can further augment allostatic load. Chronic allostatic load then leads to neural adaptations over time that increase baseline arousal while impeding one's ability to shift out of a high-arousal state. Such heightened arousal induces behavioral changes that favor short-term reward and safety but ultimately encourage poor lifestyle choices, thus perpetuating stress and allostatic load over time. CRF, corticotropin-releasing factor; HPA, hypothalamic-pituitary-adrenal; LC, locus coeruleus; NE, norepinephrine; PFC, prefrontal cortex.

A Brain-Body Approach to Chronic Disease

Though the picture painted above may seem dismal, it is far from hopeless: the same neural plasticity perpetuating allostatic load can be harnessed to facilitate more favorable adaptations conferring resilience. However, given the integrated nature of the brain-body system in allostasis, effective recovery from chronic high arousal entails more than medication. In fact, common use of pharmacological treatments for chronic disease, although sometimes necessary, proves problematic: given the origins of chronic disease lie in system-wide allostatic changes, a body-based approach employing medicine to treat peripheral symptoms is fundamentally flawed (Schulkin and Sterling 2019). Use of medication to "fix" one symptom or subsystem inherently perturbs the others, leading to compensatory adaptations that often warrant additional medications. Accordingly, the most effective treatment for chronic disease is not medication, but rather macro-scale lifestyle modifications that reduce allostatic load and strengthen parasympathetic tone. Depending on the individual, these modifications may include changes or reduction in technology use, dietary or exercise interventions, improvements in sleep, and/or incorporation of stress-reduction techniques (see Table 2.3 for summary).

Technology

To reap the benefits of technology while avoiding its pitfalls, it is important to practice moderation and mindfulness. Overall, research suggests more positive outcomes during active phone usage compared to using one's phone passively or as a means of procrastination or distraction (Verduyn et al. 2017; Dienlin and Johannes 2020). Turning to the phone or internet to cope with negative feelings (Flynn et al. 2020), to compare oneself with others (Schmuck et al. 2019), or to consume negative content (Buchanan et al. 2021; Shabahang et al. 2023) can also impair wellbeing and should be avoided. In addition, abstaining from nighttime scrolling can help prevent sleep disturbances associated with late-night usage (Levenson et al. 2017). Instead, using technology in service of social interactions has been found to enhance mental health by fostering genuine connection with others (Seabrook et al. 2016; Verduyn et al. 2017; Clark et al. 2018). Regular voice communication, for instance, correlates with stronger bonds (Chan 2015). Moreover, employing phone applications that promote productivity, fitness, health, or stress-relief can help reinforce healthful behaviors (Higgins 2016; Hwang and Jo 2019); and time saved with online shopping or virtual meetings can be repurposed for more enjoyable activities, like time in nature or with friends.

Diet

A well-balanced, diverse diet of minimally processed foods can improve overall health while preventing overeating and obesity. For example, the Mediterranean (Sofi et al. 2008; Sánchez-Sánchez et al. 2020), MIND (Arjmand et al. 2022; Corley 2022), and DASH (Siervo et al. 2015; Lari et al. 2021) dietary patterns have demonstrated favorable outcomes in both observational studies and interventions. These diets all favor consumption of fruits, vegetables, beans, protein, seafood, and whole grains while limiting refined grains, sodium, added sugars, and saturated fats. Similar dietary patterns are associated with lower allostatic load (Mattei et al. 2011; Kusano et al. 2016; Soltani et al. 2018; Suvarna et al. 2020). Additionally, prioritization of leafy green vegetables and berries may potentially reduce chronic disease and support cognitive health (Zafra-Stone et al. 2007; Devore et al. 2012; Morris et al. 2018; Kumar et al. 2020) – presumably due to their high concentrations of antioxidants, micronutrients, and fiber. Omega-3 fatty acids are also commonly emphasized in healthful dietary patterns, conferring a wide array of benefits, such as reduced inflammation (Kavyani et al. 2022), improved heart and brain health (Derbyshire 2018; Hu et al. 2019), lower cortisol levels (Delarue et al. 2003; Barbadoro et al. 2013), and better mood and cognition (Grosso et al. 2014; Kosti et al. 2022).

Greater consumption of unprocessed or minimally processed foods, as is common in the Mediterranean, MIND, and DASH diets, can provide additional advantages by enhancing satiety to reduce overeating. Whereas highly processed foods are designed to be hyperpalatable and easy to overconsume (Rolls et al. 2020), less processed foods typically contain more water and fiber, which enhance satiety (Holt et al. 1995) while providing fewer calories for comparable volume. In addition, eating protein sources like lean meat, seafood, and low-fat dairy can further support satiety while promoting optimal body composition (Paddon-Jones et al. 2008; Veldhorst et al. 2008). Regarding the latter, amino acids in dietary protein prove essential for the growth and repair of muscle and all bodily tissues; daily protein intake of 1.4-2.0 grams per kilogram of body weight can best support muscle preservation or gain (Jäger et al. 2017). Recent research reports muscle to offer various health-promoting benefits due to its uptake of glucose and release of myokines (Merz and Thurmond 2020; Rai and Demontis 2022) – among other mechanisms – suggesting it is an underappreciated contributor to health and longevity (Wolfe 2006).

Beyond satiety, consumption of fiber is also crucial for cardiometabolic health (Weickert and Pfeiffer 2008; Riccioni et al. 2012) and for maintaining a healthy gut microbiome. Healthy gut bacteria feed on fiber, which they ultimately ferment to produce short-chain fatty acids (SCFAs). SCFAs have anti-inflammatory properties; protect against diabetes and obesity; and support cardiovascular, brain, and liver health (Xiong et al. 2022). Increasing evidence also suggests that fermented foods can positively affect both gut and overall health (Diez-Ozaeta and Astiazaran 2022; Leeuwendaal et al. 2022). Interestingly, omega-3 fats appear to benefit gut microbiota as well (Costantini et al. 2017). In addition to incorporating these nutrients and foods, eating a diverse diet has been found to support a more diverse and resilient microbiome (Heiman and Greenway

2016).

Nonetheless, one's mindset and approach toward food can also influence nutrition and dietary choices. For example, practicing mindful eating may potentially improve food intake regulation to facilitate weight management or loss (Warren et al. 2017). Meanwhile, adopting a flexible mindset that encourages moderation and leaves no food *off-limits* can prevent episodes of binging and foster a healthy relationship with food (Smith et al. 1999; Stewart et al. 2002). Thus, a truly healthy diet need not shun all processed foods, but rather can incorporate them sparingly according to personal preferences. Such an approach yields greater long-term success and adherence, as one is more likely to follow a diet they enjoy.

Physical Activity

Incorporating physical activity – both in the forms of aerobic and resistance training – is crucial for reducing allostatic load and improving parasympathetic tone. Though most of the research has examined the effects of aerobic exercise (or "cardio"), both cardio and resistance training can improve brain structure and function, especially in the frontal lobe and hippocampus (Erickson et al. 2014; Feter et al. 2018; Herold et al. 2019). Correspondingly, better cognition (Landrigan et al. 2020; Zhang et al. 2023), memory (Loprinzi et al. 2018, 2020), wellbeing (Fox 1999; Windle et al. 2010; Gordon et al. 2017), and executive functioning (Guiney and Machado 2013; Zhang et al. 2023) have been observed in response to such exercise interventions. Additionally, strong evidence indicates that cardio can improve heart-rate variability (HRV) and vagal tone (Grässler et al. 2021; Souza et al. 2021). Similar investigations of resistance training have been less conclusive in healthy individuals, with improved HRV seen primarily in diseased populations (Bhati et al. 2019). Regardless, resistance training can boost cardiometabolic health by reducing resting blood pressure, improving blood lipid profiles, and enhancing insulin sensitivity (Westcott 2012). Moreover, resistance training enables muscle gain and preservation, which proves particularly important for fat loss (Hunter et al. 2008; Kirk et al. 2009). Accordingly, a combination of resistance training and cardio results in better body composition and overall health than aerobic activity alone (Marzolini et al. 2012; Villareal et al. 2017; García-Hermoso et al. 2018).

However, physical activity is more than exercise: it also includes movement throughout the day, at home and in the workplace (Caspersen et al. 1985; Katzmarzyk 2010). Benefits of regular exercise can, to some extent, be offset by sedentary behavior (Kulinski et al. 2014); and a generally active daily life is associated with better cardiovascular health and longevity, independent of exercise (Ekblom-Bak et al. 2014). Thus, incorporating more non-exercise activity throughout the day can support overall health and lower allostatic load. Increasing non-exercise activity can also contribute to greater total daily energy expenditure and help support weight loss and maintenance (Levine 2002). Simple ways to increase non-exercise activity include engaging in housework and chores, standing instead of sitting, and walking during phone calls.

Daily walking provides an easy way to improve cardiovascular and overall health. For instance, walking is associated with improved aerobic fitness, better blood pressure, lower adiposity, better mental health, and greater longevity (Robertson et al. 2012; Murtagh et al. 2015; Saint-Maurice et al. 2020). Moreover, a recent meta-analysis reported that greater daily steps correlate with a progressively lower risk of all-cause mortality up to 6000-8000 steps for populations 60+ and 8000-10000 for those under 60 years old (Paluch et al. 2022). Given walking is simple, low-risk, and often enjoyable, it offers an easy avenue into exercise for individuals of all ages and at all levels of experience.

A broad array of activities can satisfy physical activity recommendations and subsequently improve health. As a result, there is no one best exercise regime, and individual preference plays a key role in making movement a habit. In addition to practicing a personally enjoyable exercise modality, one can promote exercise adherence by incorporating an element of social accountability or support (Fry and Neff 2009; Greaney et al. 2018) and by occasionally introducing novelty to keep workouts fun (Lakicevic et al. 2020). Moreover, applying temptation bundling by pairing exercise with an intrinsically pleasurable activity (i.e., using a cardio machine while watching television) can further encourage frequent exercise (Kirgios et al. 2020).

Sleep

Seven to nine hours of sleep is generally recommended for adults, with adolescents in need of eight to ten hours nightly (Hirshkowitz et al. 2015). However, sleep quality is just as important – if not more – than sleep duration (Kohyama 2021); and a variety of factors have been found to affect both. Overall, the literature highlights the influence of light exposure, sleep regularity, sleep environment, stress and affect, stimulant and alcohol use, and exercise on sleep. Improving sleep hygiene by addressing these factors provides promise in promoting quality sleep.

Light is a well-established *zeitgeber* that can entrain the circadian rhythm (Blume et al. 2019). As such, both exposure to daylight and avoidance of artificial blue light at night can best support sleep. Getting morning sunlight can help regulate production of cortisol and melatonin (Leproult et al. 2001); and general exposure to outdoor light during the day correlates with better sleep quality (McAlpine et al. 2023; Boubekri et al. 2014). In contrast, exposure to artificial blue light at night for prolonged periods may disrupt sleep by interfering with melatonin production (Gooley et al. 2011; Šmotek et al. 2020). Accordingly, reducing exposure to blue light at least two hours before going to bed is more conducive to sleep. Given the prevalence of screens and lights, blue-light blocking lenses may offer an easy means of doing so (Guarana et al. 2021), although evidence supporting their utility is mixed (Shechter et al. 2020).

Going to bed and waking at variable times each night is associated with poorer sleep quality, reflecting the importance of regularity in sleep (Irish et al. 2015; McAlpine et al. 2023). Regular sleep-wake schedules have been found to improve sleep quality and reduce daytime sleepiness, even when sleep length is equated (Manber et al. 1996). In addition to maintaining a regular sleep schedule, creating a relaxing sleep routine can help induce a low-arousal state favorable for sleep (Mindell et al. 2015; Koketsu 2018).

Establishing a comfortable and relaxing sleep environment also correlates with better quality sleep. Having a comfortable bed and pillow and keeping one's sleep environment dark, quiet, cool, and well-ventilated can support sleep (Caddick et al. 2018). Moreover, using one's bed for activities other than sleep is associated with worse sleep quality and should be avoided, as should lying in bed restless (Bootzin et al. 1991). In the case of the latter, it is generally recommended that one engage in a relaxing activity out of bed until they feel sufficiently sleepy.

Feeling stressed both at night and chronically has been found to negatively affect sleep, presumably due to induction of a high-arousal, negative affect state counterproductive to relaxation (Irish et al. 2015; McAlpine et al. 2023). Similarly, perseverative cognition is negatively associated with sleep quality (Van Laethem et al. 2016; Clancy et al. 2020). Interventions that reduce stress levels and rumination, such as mindfulness and cognitive-behavioral therapy, have demonstrated benefits for sleep (Friedrich and Schlarb 2018; Rusch et al. 2019).

While research examining the effects of stimulants and alcohol shows conflicting findings (Irish et al. 2015; McAlpine et al. 2023), a mechanistic understanding of these compounds indicates a potentially negative impact on sleep (Nehlig et al. 1992; Thakkar et al. 2015). Having caffeine in the evening may impair sleep (Drake et al. 2013) due to its approximately five-hour half-life (Institute of Medicine (US) Committee on Military Nutrition Research 2001) – though individual differences and habituation may moderate its effect (Kalow 1985). Meanwhile, alcohol intake can increase the risk of obstructive sleep apnea and reduce REM sleep at high doses, with effects at lower doses less consistent (Ebrahim et al. 2013; Kolla et al. 2018; Burgos-Sanchez et al. 2020).

Lastly, regular exercise, both in the form of aerobic and resistance training, has been found to benefit sleep (Kredlow et al. 2015; Dolezal et al. 2017; Kovacevic et al. 2018). Specifically, research reports exercise-related improvements in sleep time, efficiency, onset latency, and quality. Most studies observe such benefits regardless of exercise timing, with little evidence that evening exercise impairs sleep (Stutz et al. 2019). Nevertheless, it is plausible that vigorous exercise within an hour of bedtime may adversely affect sleep and should be avoided.

Perceived Stress

A variety of strategies have been found to effectively reduce perceived stress and markers of allostatic load, ranging from mind-body approaches to time in nature. Regarding the former, breathwork has proven effective at reducing psychological and physiological measures of stress (Zaccaro et al. 2018; Laborde et al. 2022; Banushi et al. 2023; Bentley et al. 2023), both as an isolated intervention and when incorporated into practices like yoga and Pilates. The breath provides a means by which one can consciously regulate the autonomic nervous system, as autonomic balance shifts as a function of respiratory phase (Eckberg et al. 1985). Breathing can also influence brain state through respiratory entrainment of neural oscillations, observed both in the hippocampus and cortex (Lockmann et al. 2016; Lockmann and Tort 2018). Accordingly, research on slow breathing reports modulations of brain spectral activity and heart rate variability consistent with greater parasympathetic activity (Zaccaro et al. 2018). Nonetheless, a more recent systematic review suggests that a wide array of breathing practices can ameliorate perceived stress and anxiety, with the exception of fast-only breathing (Bentley et al. 2023).

Controlled breathing integrated with movement practice, as in yoga and Pilates, may further alleviate stress by fostering a gentle attunement to one's bodily position and sensations. Interventions of both benefit mental health, improving mood and reducing depression and anxiety symptoms (Fleming and Herring 2018; Martínez-Calderon et al. 2023). More specifically, yoga asanas have been found to improve physiological stress measures like cortisol, blood pressure, heart rate, and heart rate variability (Pascoe et al. 2017). These benefits extend to the brain, with greater PFC and hippocampal volume observed in yoga practitioners (Gothe et al. 2019).

Mindfulness, particularly when combined with yoga and body awareness as is done in mindfulness-based stress reduction (MBSR), has been extensively researched and validated as a tool for stress relief (Reive 2019). Overall, MBSR has been found to reduce subjective measures of stress and anxiety (Khoury et al. 2015) along with blood pressure (Conversano et al. 2021). Neural changes, such as decreased activity in the amygdala, increased activity in the PFC, and increased volume and activity in the hippocampus have also been reported (Reive 2019). While the majority of mindfulness research employs MBSR, isolated mindfulness practice – in which one focuses attention nonjudgmentally on present experience – may also improve wellbeing (Zollars et al. 2019), lower anxiety and stress (Bamber and Morpeth 2019; Bostock et al. 2019), increase heart-rate variability (Krygier et al. 2013), and reduce cortisol (Heckenberg et al. 2018).

Spending time outdoors may help relieve stress as well, with exposure to green space associated with lower stress levels (Zhang et al. 2020; Yao et al. 2021). These subjective markers are complemented by physical changes, such as decreased cortisol, heart rate, and blood pressure (Yao et al. 2021). The stress-reduction benefits of nature may derive from its relatively low-arousal environment, which may provide respite from high-arousal, information-rich urban milieus (Berto 2014). Given the importance of natural light exposure for circadian physiology, increasing time in nature may also reduce allostatic load by supporting sleep. Moreover, performing breathwork, yoga, or mindfulness outdoors may further magnify these benefits.

Table 2.3: Lifestyle factor recommendations to reduce allostatic load and enhance resilience. Through behavioral modifications addressing technology use, diet, physical activity, sleep, and stress management, one can alleviate chronic stress and allostatic load. CBT, cognitive behavioral therapy.

Lifestyle Factor	***What to do***	***What to avoid***
Technology	• Use intentionally, actively, in moderation • Support genuine social connection • Regular voice communication • Applications that scaffold healthful behaviors (i.e., productivity, fitness, health, stress-relief apps)	• Passive use or as procrastination • Use to cope with negative emotions • Negative content • Social comparisons • Nighttime scrolling • Replacing in-person interactions with written messages
Diet	• Balanced, diverse diet • Minimally processed foods: fruits, vegetables, legumes, seafood, lean meats, & whole grains • Leafy green vegetables & berries • Sources of omega-3 fatty acids: salmon, tuna, mackerel, sardines • High-protein & high-fiber foods • Mindful eating & moderation	• Ultra-processed, hyperpalatable foods • High saturated fat intake • Mindless or emotional eating, overeating
Physical Activity	• Regular aerobic activity: walking, running, "cardio" machines • Regular resistance training: weightlifting or calisthenics • Movement throughout the day • 6000+ steps/day	• Prolonged, regular sitting • Physical inactivity • Excessive exercise or overtraining
Sleep	• 7-10 hours of sleep nightly • Regular sleep schedule • Exposure to natural daylight outdoors • Relaxing sleep routine • Comfortable, cool, dark, well-ventilated sleep environment • Leave bed if unable to sleep • Mindfulness or CBT • Regular exercise	• Blue light exposure at night • Variable sleep-wake times • Using the bed for work, phone use, or any waking activity • Lying in bed restless • High psychological stress at night • Caffeine or alcohol in the evening
Perceived Stress	• Slow regulated breathing • Yoga or Pilates • Mindfulness • Spend time outdoors • Arts & other wellness activities	• Cognitive distortions • Perseverative cognition • Overwork

Adopting a Healthy Lifestyle: Science of Behavior Change

While a multipronged approach to alleviating allostatic load incorporates modifications in technology use, diet, exercise, sleep, and stress management, effective change at the individual level must start conservatively. The self-perpetuating cycle of arousal pathology can create a sense of "being stuck," in which such change may seem overwhelming or even impossible. Progressive weakening of the PFC and strengthening of subcortical regions favor habitual and reward-driven behavior, which can preclude behavioral changes that rely on sustained willpower and self-control. As a result, creating a healthy lifestyle through habit formation offers a more successful and sustainable approach. It is important that these to-be-habitual behaviors are sufficiently small and realistic, as habit formation demands consistent and repeated performance (Wood and Neal 2016). Fortunately, a resounding theme across various healthy behaviors – from breathwork (Bentley et al. 2023) and mindfulness (Strohmaier 2020) to exercise (Islam et al. 2022) – is that significant benefits accompany even a few minutes of practice. In addition, modifying one's environment (Wood et al. 2005; Schüz et al. 2015) and finding enjoyment in healthy behaviors (Gardner and Lally 2018) can further support the consistency needed for habit formation. For instance, stocking up on more nutritious foods, creating a home gym, or purchasing a standing desk can help encourage better dietary choices and physical activity; while avoiding purchasing hyperpalatable foods and moving the television outside of the bedroom can discourage overeating and blue-light exposure prior to sleep, respectively. Since one's social environment can have similarly strong influence (Zimmerman and Connor 1989; Robinson et al. 2013), surrounding oneself with health-oriented and supportive individuals can further foster behavior change. Moreover, given the variety of effective diets, exercise regimes, and stress-management strategies, one can select those that best suit their personal preferences; and doing so can support long-term adherence by kindling intrinsic motivation (Ryan et al. 1997; Gardner and Lally 2018). Lastly, the interconnectedness of health behaviors may give rise to a snowball effect, in which engagement in one health-promoting behavior ultimately leads to engagement in others (Figure 2.5). These mutually reinforcing behaviors arise from their common effects on the brain and body via reduction in allostatic load, strengthening of the PFC, and enhanced self-regulation.

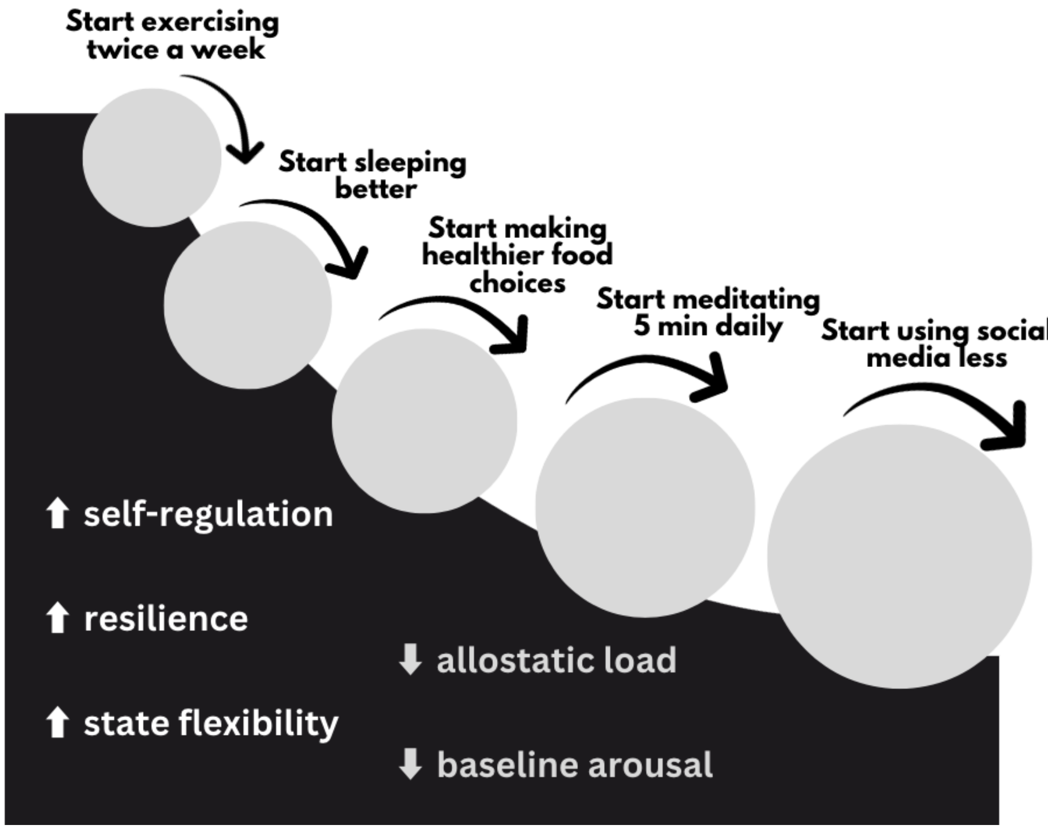

Figure 2.5: An example of the lifestyle-related snowball effect. Small but consistent changes in behavior feed into one another, incrementally increasing self-regulation, resilience, and state flexibility while reducing allostatic load and baseline arousal. For instance, simply by starting an exercise routine, one may notice an improvement in sleep; and both exercise and sufficient sleep improve appetite regulation and decision making, which may lead to healthier food choices. Improved self-regulation from these cumulative changes may then encourage adoption of other healthful behaviors, such as a daily meditation practice. As self-regulatory capacity continues to increase, reduced tendency toward reward-driven behaviors and addiction may also decrease use of social media. min, minute.

Conclusion

The ability to flexibly adjust and coordinate arousal state with the environment is crucial for adaptive behavior and survival. Such arousal shifts are mediated by an extended autonomic system that implicates both brain and body through integration of the central autonomic network and autonomic nervous system. Under optimal conditions, this integrated system enables autonomic flexibility; however, experiences and lifestyle can influence this flexibility via allostatic adaptations. While allostatic changes favoring high arousal may enable adaptive responses to short-term stressors, unfavorable adaptations occur in the context of chronic arousal or stress. In the case of the latter, a chronic high-arousal allostatic state leads to arousal pathology and autonomic inflexibility, in which strengthening of the sympathetic nervous system and subcortical structures alters the proportionality of brain functioning. This chronic state shift is exacerbated by feedforward connections, breakdown of negative feedback, and runaway excitation – leading to a self-perpetuating cycle that precludes return to a lower arousal baseline. Crucially, the chronic arousal that leads to such pathology extends beyond perceived stress to encompass lifestyle factors and health risk behaviors, such as excessive technology use, physical inactivity, poor diet, and sleep deprivation; and these behaviors are particularly common in modern society. Accordingly, today's rise in chronic disease and mental health crises may derive from allostatic load and arousal pathology; and the only effective means of ameliorating these issues lies in addressing the behaviors and environment inducing chronic physiological and psychological stress. Though breaking the vicious cycle of high arousal can prove difficult, even small improvements in lifestyle can snowball into a positive self-sustaining cycle of resilience, strengthening parasympathetic tone and the PFC to enable better self-regulation, decision-making, and overall health.

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Chapter 3 STRESSED AT REST: MODULATION OF RESTING-STATE ACTIVITY AND EVOKED POTENTIALS BY ALLOSTATIC LOAD

Abstract

The ability to dynamically coordinate our brain and behavioral state with external demands is crucial for fluid functioning in an ever-changing environment. However, such dynamic attending may be affected by chronic stress, which alters brain structure and function over time, favoring a hypervigilant cortical state with heightened responsiveness to unexpected events. Electroencephalography (EEG) may provide a macroscopic means of probing these neural changes via individual differences in neural oscillations at rest and in evoked potentials to irregularly timed stimuli. The current study thus examines the interplay between chronic stress burden, or *allostatic load*, resting-state oscillatory activity, and evoked potentials to temporally predictable and unpredictable stimuli. We measured allostatic load in undergraduate college students using questionnaires assessing health risk behaviors and wellbeing, subsequently recording resting-state EEG and N1P2 evoked potentials during a passive temporal auditory oddball task. Participants with higher allostatic load scores exhibited greater resting-state alpha and beta oscillatory power but did not differ significantly in evoked responses. Our findings indicate that individual differences in resting-state spectral activity may reflect allostatic load arising cumulatively from poor sleep, low-quality diet, physical inactivity, excessive technology use, and high psychological stress.

Introduction

Our experience of and interaction with the world is fundamentally structured in time. As such, temporal processing enables fluid functioning in an ever-changing environment, facilitating bodily movement (Ashoori et al. 2015), speech comprehension (Assaneo et al. 2019), and social interactions (Schirmer et al. 2016). Moreover, dynamic coordination of endogenous fluctuations in arousal with external rhythmicity offers an adaptive, energy-efficient strategy whereby one can ignore or "tune out" unimportant regularities while "tuning in" to relevant regular or unexpected events that may pose threat or opportunity (Schafer 1982).

Temporal processing deficits have been observed in a variety of neurological disorders, like attention deficit hyperactivity disorder (Toplak et al. 2006; Khalil et al. 2013), schizophrenia (Carroll et al. 2009), autism spectrum disorder (Stevenson et al. 2016; Meilleur et al. 2020), dementia (Rabinowitz and Lavner 2014), Parkinson's disease (Roalf et al. 2018), and dyslexia (Meilleur et al. 2020). In neurotypical individuals, temporal processing can vary as a function of diverse factors, from musical experience to arousal level. For instance, musical training has been found to enhance sensorimotor synchronization (SMS; Repp 2010), duration discrimination (Banai et al. 2012), and temporal estimation (Panagiotidi and Samartzi 2013). Meanwhile, high arousal increases spontaneous motor tempo (Hammerschmidt and Wöllner 2023) and induces temporal dilation (Cui et al. 2023), in which time appears to pass more slowly. This temporal distortion purportedly provides an advantage under threat by creating more subjective time to approach, attack, or flee (Cui et al. 2023).

In a previous study, we assessed temporal processing in both behavior and electroencephalography (EEG) through an SMS task and a passive temporal auditory oddball paradigm, respectively (D'Andrea-Penna et al. 2020). The former required participants to tap on drums in synchrony with an external rhythm, while the latter involved passive listening to streams of regularly and irregularly timed beats. During the passive listening portion, we measured the N1-P2 complex, a brain evoked potential (EP) that reflects early sensory processing (Remijn et al. 2014) but is modulated by higher-level processes, including temporal expectancy (Schafer et al. 1981; Todorovic and de Lange 2012; Kononowicz and van Rijn 2014; Duzcu et al. 2019; Menceloglu et al. 2020). We observed that participants with better SMS demonstrated a larger N1-P2 differential to deviant versus expected stimuli during passive listening. We therefore proposed this differential to be a neural marker of temporal processing, which we termed the timing response index (TRI). The TRI, as a passive marker, could help detect temporal processing deficits in clinical and subclinical populations, with particular utility in those whose behavioral response may be unreliable.

However, arousal and stress may modulate evoked potentials through allostatic mechanisms and consequently moderate the relationship between the TRI and SMS. States of high arousal and stress involve an influx of catecholamines, such as norepinephrine and dopamine, to the cortex, as well as widespread release of cortical acetylcholine. These neuromodulatory changes induce a hypervigilant cortical state characterized by enhanced neural responsiveness to unexpected events, as has been observed both clinically, in individuals with post-traumatic stress disorder (PTSD) and panic disorder (Chang et al. 2015; Bangel et al. 2017; Zukerman et al. 2018), and subclinically, in those with high trait anxiety and low resilience (Ding et al. 2022; Ioakeimidis et al. 2023). Given that evoked potentials arise from interactions between sensory stimuli and ongoing endogenous activity, arousal may exert such effects by modulating resting state dynamics. Perhaps not surprisingly, arousal and stress have also been found to alter resting state spectral power, although findings vary in the precise effects: some find increases in alpha (Knyazev et al.

2004; Komarov et al. 2020) and beta (Díaz M. et al. 2019) power, whereas others report reduced alpha power (Vanhollebeke et al. 2022).

Allostasis, proposed by Sterling and Eyer to explain arousal pathology, provides an integrative framework in which summative stressors exert widespread effects on the brain and body through the stress response (Sterling and Eyer 1988). Importantly, both psychological and physiological forms of stress activate the same allostatic mechanisms (McEwen 2008). Cumulative stress burden, or "allostatic load," is thus composed of both psychological distress and health risk behaviors, including poor diet, physical inactivity, insufficient sleep, and excessive technology use (Dienlin and Johannes 2020; Suvarna et al. 2020). While modern lifestyle often encourages such stressors, the recent COVID-19 pandemic has further exacerbated allostatic load, disrupting day-to-day living and increasing social isolation (Cianfarani and Pampanini 2023).

Accordingly, the current study assessed the contributions of allostatic load to resting-state and timing-related brain activity. Similar to D'Andrea-Penna et al. (2020), participants first attempted to synchronize their tapping with an external beat, after which they passively listened to a temporal auditory oddball paradigm during EEG data acquisition. Here, passive listening included blocks of silence for resting state data, from which we examined individual differences in alpha oscillatory power, the most prominent feature of baseline EEG. Lastly, through questionnaire data we probed emotional wellbeing and lifestyle choices associated with allostatic load. Consistent with the known effects of stress on neuromodulation and vigilance, we hypothesized that resting-state alpha power and allostatic load would correlate both with the TRI and with one another. More specifically, we predicted that individuals with higher allostatic load would demonstrate lower resting-state alpha power due to greater baseline arousal levels; and that those with lower alpha power and/or higher allostatic load would exhibit a larger TRI due to stress-induced hypersensitivity to unexpected stimuli.

Materials and Methods[2]

Participants

Forty-two participants between ages 18 and 22 (mean 20 years, 31 female and 11 male) were recruited from the University of California, San Diego. Two participants were excluded from the analysis due to excessive noise and artifacts in their EEG data. All participants provided written consent, and this study was approved by the Institutional Review Board of the University of California, San Diego.

Stimuli & Procedure

Participants first completed the tapping task, then answered questionnaires, and, lastly, partook in passive listening during EEG acquisition. For both the tapping task and passive listening session, participants heard rhythmic streams of tone bursts from a speaker (~75 dB, SPL). Each burst consisted of an 800-Hz sine pulse, 50 ms in duration with a 10-ms ramp up and ramp down to avoid clicks at onsets and offsets.

Tapping Task

Participants tapped individually for two minutes, attempting to synchronize with isochronous beats. For the tapping task, beats were separated by a 600-ms interonset interval (IOI), a relatively comfortable pace for sensorimotor synchronization (Repp 2005). Beats were occasionally omitted (15% probability); however, participants were instructed to maintain the basic rhythm while tapping and to tap where the beat should be, despite the omissions. Participants

[2] A substantial portion of the methods section derives from D'Andrea-Penna et al. (2020).

tapped onto wood blocks affixed to drums at approximately lap height, under which piezoelectric sensors were placed to record their taps as *.wav* files into Adobe Audition.

Questionnaire Data Collection

Participants were asked to complete an allostatic load survey and the Harvard Flourishing questionnaire.

Allostatic Load Survey

We designed an allostatic load survey using a Likert scale with 4 or 5 response options per question (see Appendix for survey items). Given the influence of lifestyle choices on allostatic load and overall health, we incorporated questions about sleep duration and quality, dietary choices, physical activity levels, emotional wellbeing, and technology use. For instance, participants were asked, “How much sleep do you get each night?” and “How often do you have trouble falling asleep or staying asleep?” as part of the sleep section; “How many servings of fruits and vegetables do you consume daily?” and “How often do you consume fast food?” with other diet-related questions; “How often do you engage in regular aerobic activity each week?” and “How physically active are you throughout the day?” under physical activity; “How often do you feel anxious?” and “How often do you feel overwhelmed?” in the wellbeing questions; and “How often do you use your phone per day?” and “ How often do you visit social media apps & sites daily?” in the technology section. To develop a gross allostatic load score, responses to individual questions were first normalized to a common scale and reverse ordered if needed such that higher scores indicated greater allostatic load (i.e., health risk behaviors leading to worse sleep, lower diet quality, less physical activity, poor mental health, and greater technology use). Subsequently, each section was normalized to a common scale and all section scores summed, yielding a single allostatic load score for each participant that ranged from 0 to 5.

Flourishing Questionnaire

The secure flourish index, developed by the Human Flourishing Program at Harvard University (VanderWeele 2017), was included as a more standardized measure of resilience and allostatic load. This index derives from a Likert scale of 12 questions addressing various domains of human wellbeing: happiness and life satisfaction, mental and physical health, meaning and purpose, character and virtue, close social relationships, and financial and material stability. Responses ranged from 0 to 10, with a response of 10 indicating highest flourishing – here interpreted as lowest allostatic load. The secure flourishing index averaged all 12 responses, leaving a minimum possible score of 0 and maximum score of 10.

Passive Listening

A 35-minute passive listening session followed the tapping task (Figure 3.1). To avoid the confound of sensory adaptation, in which EP amplitude decreases with shorter inter-onset intervals (Rothman et al. 1970), we used a two-condition paradigm consisting of two trial types that were presented alternately 8 times, for a total of 16 trials. The "long condition" used an 800 ms IOI, with rare extra beats occurring at a 400 ms IOI (halfway between surrounding 800-ms IOI beats, 15% probability). The "short condition" used a 400-ms IOI, with rare omissions (15% probability). These two conditions strategically allowed for identical stimulus sequences in which the same two IOI's preceded the key sound to which the evoked brain response was measured (either an extra beat in the long condition or a standard in the short condition), controlling for adaptation such that only their expectancy differed. Henceforth the extra beats in the long condition will be referred to as "deviants" and the sequence-matched, expected beats in the short condition will be called "standards." Resting periods with 60 s of silence were interwoven between each block of beats for

6 times, providing 6 minutes total of baseline EEG data. Thereafter, blocks of the long and short conditions continuously alternated until the end of the recording.

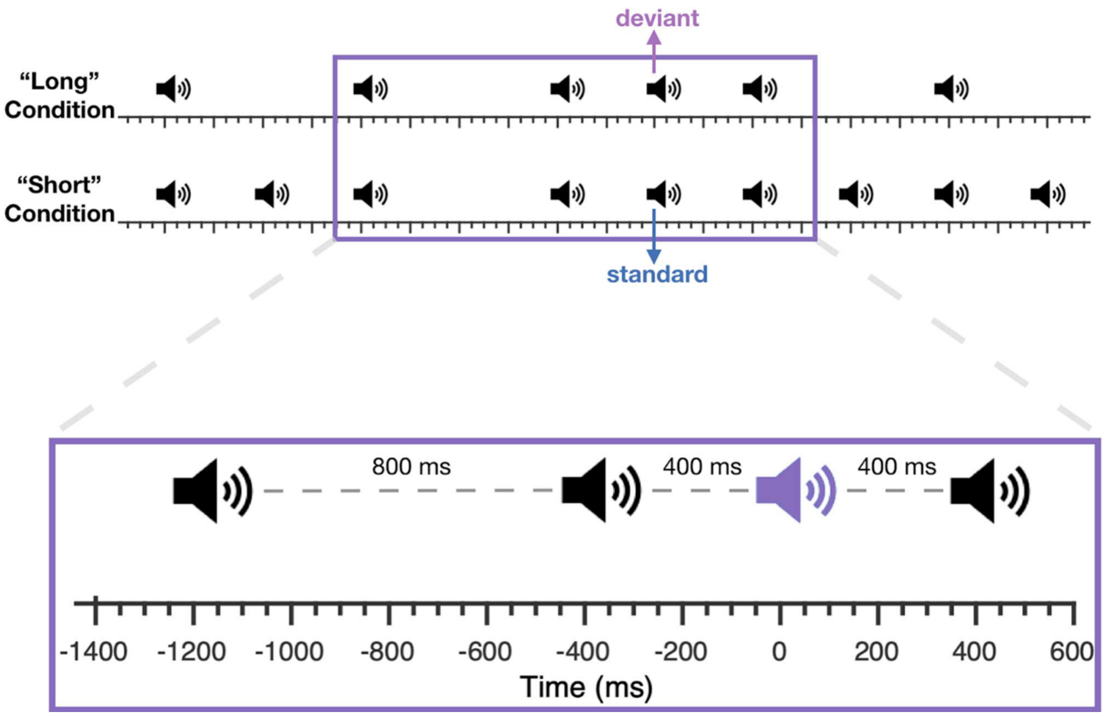


Figure 3.1: Passive listening temporal oddball paradigm. Participants passively listen to streams of sounds in 2 conditions. The "long" condition includes isochronous beats that are sometimes interrupted by an unexpected beat ("deviant"). The "short" condition is twice as fast as the long condition and contains occasional omissions. This arrangement allows us to compare brain responses with deviants and standards, which are physically the same sequence of stimuli to control for neural adaptation (see Methods) but vary in temporal expectancy. *Figure and caption from D'Andrea-Penna et al. (2020).*

EEG Acquisition

During passive listening, participants wore a 10-channel EEG cap containing electrodes at Fp1, Fz, Cz, C3, C4, T7, T8, Pz, Oz, and M1. Due to equipment failures, ten participants did not have data for M1, two lacked Oz, one lacked C3, and two lacked T7 and T8. One frontal electrode served as ground, and EEG data was referenced online to C4 but later re-referenced to the average of all available channels. Signal quality was inspected prior to recording: all impedances were below 25 kΩ. An additional channel fed by a microphone was sent into the EEG interface to enable event coding with temporal precision. Data was recorded at 2000 Hz.

Analysis

Tapping

Vector Strength

An average of 202 taps was recorded per participant (range 171 to 316). Tapping time series (of strike times) underwent a vector strength (VS) analysis, which provided a measure of each participant's ability to synchronize with the external rhythm -- particularly of their ability to tap with a consistent phase relative to the driving beat. VS is defined as:

$$\mathrm{VS} = \frac{1}{N} \left| \sum_{j=1}^{N} e^{i\phi j} \right|$$

where N is the total number of taps by one participant, ϕj is the tap phase relative to the driving rhythm for tap number j, and i is the imaginary unit. Accordingly, VS is 1 if a tapper is perfectly consistent, maintaining the same phase of tap strikes relative to the phase of the auditory stimuli, and 0 if the participant taps randomly (Khalil et al. 2013).

Standard Deviation of the Inter-Tap Interval (ITI)

Upon examining tapping patterns, we observed that some participants who were poor synchronizers were nonetheless rhythmic tappers. As a result, we also included the standard deviation of inter-tap intervals as a secondary measure of tapping ability. Standard deviation of the time intervals between each participant's taps was calculated to assess tapping regularity independent of the external rhythm.

EEG

General Preprocessing

EEG data was processed and analyzed using EEGLAB (Delorme and Makeig 2004). After identifying the different types of events (standard and deviant beats) using the microphone channel, resting state data was extracted for separate analyses and both data were downsampled to 500 Hz. Manual inspection guided rejection of noisy channels prior to re-referencing, during which M1 was removed from five participants and Fz from another.

N1-P2 EP Preprocessing

Data were selected from the Cz electrode site, consistent with D'Andrea-Penna et al. (2020) and other studies examining the N1-P2 complex (Hillyard et al. 1973; Schafer et al. 1981). High-pass and low-pass Hamming windowed sinc FIR filters with cutoff frequencies of 0.1 and 30 Hz were applied to the data prior to event selection and epoching. The deviant and standard beats (see Figure 3.1) were selected, epoched, and baseline corrected to the 50 ms period preceding the beat. Initially there were 170 deviant events and 185 standard events for each participant. Automatic artifact rejection via extreme values removed trials with voltages beyond $\mp$ 30 μV, leaving a mean of 165 deviants (range 134-170) and 179 standards (range 123-185) per participant.

Resting State Preprocessing

The first and last 5 seconds of each resting state block were trimmed to mitigate potential confounds associated with the transition between the auditory oddball stimuli and silence. Channels Cz and Oz were selected for spectral analysis, as Cz was also used for the N1-P2 analysis and Oz tends to have strong alpha oscillations. Hamming windowed sinc FIR filters with a high-pass cutoff frequency of 0.1 and notch filtering between 59 and 61 Hz were applied to the data prior to artifact rejection. Manual inspection was then used to remove eye or muscle movements and any other artifacts. For instance, selections showing prominent voltage change in Fp1 that bled into other channels were removed, as well as were episodes containing excessive high-frequency noise, drifting, or unnaturally synchronous activity typical of mechanical artifacts. The remaining resting-state data averaged 163 s across all participants (range 42-258 s). Due to the wide range of resting-state data length, follow-up analyses were done with power spectra based on 60 s of data from each subject, excluding those with fewer than 60 s of clean data (see Supplemental Table 3.1).

TRI (N1-P2 EP Difference) Identification

The TRI was calculated in the same manner as in D'Andrea-Penna et al. (2020). Across-participant grand averaged EPs were computed for the deviant and standard beats separately, and the resulting N1 and P2 for each event type were used to determine time windows for calculating mean amplitude measures in single participants' EPs. Time windows +/- 50 ms surrounding the grand average peak for each condition were identified. Accordingly, the N1 mean amplitude for each participant was calculated between 38 and 138 ms and between 52 and 152 ms for the standard and deviant beats, respectively. The P2 mean amplitude was calculated between 82 and 182 ms for the standards and between 122 and 222 for the deviants. The N1-P2 magnitude then subtracted the N1 mean amplitude from the P2 mean amplitude, and the TRI was calculated as a within-subject "difference magnitude," subtracting the standard N1-P2 magnitude from the deviant N1-P2 magnitude (see Supplemental Figures 3.1 and 3.2 for example and for single-subject EPs).

Baseline Alpha Identification

To study neural oscillatory activity, we applied a power spectral density analysis on the baseline EEG data using the *spectopo()* function implemented in the EEGLAB toolbox (Delorme and Makeig 2004). EEGLAB's channel spectra function estimates the spectral density of the entire baseline data epoch with Welch's method (Welch 1967) via MATLAB function *pwelch()*. The resultant power spectra were then parameterized using the *FOOOF* algorithm (version 1.1.0; Donoghue et al. 2020) in Python (Figure 3.2). Settings for the algorithm were as follows: peak width limits, 1 to 8; max number of peaks, 3; minimum peak height, 0; peak threshold, 2; and aperiodic mode, fixed. Power spectra were parameterized across the frequency range 3 to 40 Hz. The largest power value for identified oscillations with center frequency between 8 and 13 Hz was selected as alpha power measures for each participant, and participants without a center frequency within this range (N = 4 for Cz, N = 2 for Oz) were assumed to lack alpha oscillatory activity and thus were given a value of 0 for alpha power.

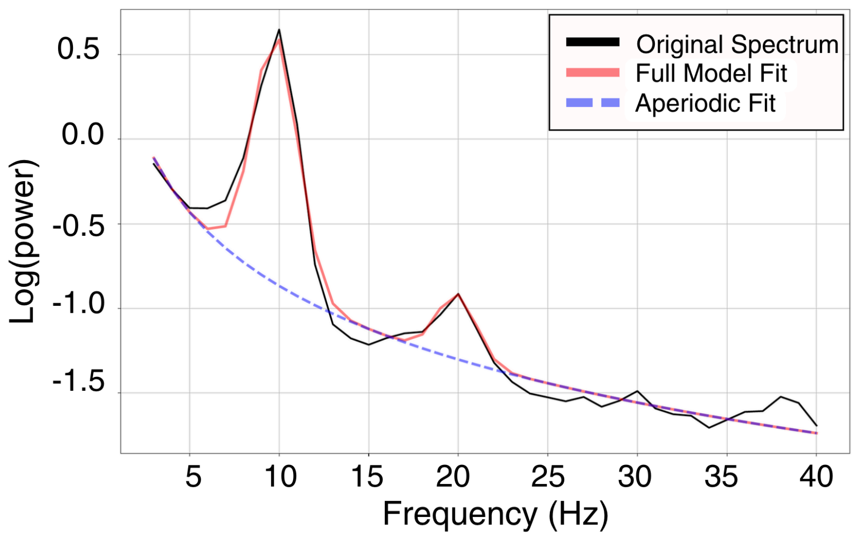


Figure 3.2: FOOOF decomposes the power spectrum to extract oscillatory and aperiodic features. Example of FOOOF fit in one participant. Black line indicates original power spectrum; red line is FOOOF model full model fit; dashed blue line is FOOOF estimate of aperiodic activity.

Resting-State Blink Identification

Since alpha oscillations are most prominent when eyes are closed, correlations with spectral data could be confounded by individual differences in eye closure across the recording. To circumvent this confound, we controlled for the total number of blinks in follow-up partial correlations with the spectral data, assuming that those with eyes closed would make fewer blinks. Using BLINKER, an automated extraction of ocular indices from EEG, we detected the total number of blinks detected in Fp1 across the entire raw resting-state recording (Kleifges et al. 2017).

Statistics

Correlational analyses

Due to multicollinearity of two different domains – tapping measures (VS and standard deviation of the ITI) and allostatic load measures (allostatic load scores and secure flourish index), we opted for correlational analyses over multivariate regression, as the latter had the potential to produce an unstable model. The relationship between TRI and alpha power, secure flourish index, allostatic load score, VS, and the standard deviation of the ITI was assessed via Spearman correlation. A Spearman correlation was also conducted between alpha power and allostatic load score and secure flourish index. All correlations with TRI were also performed with the N1 and P2 differences separately due to potential dissociations between the N1 and P2 based on prior literature and evidence suggesting distinct underlying generators (for a review, see Crowley and Colrain 2004).

T-Tests

Two-sample t-tests of the TRI of participants with the 10 highest and lowest VS, standard deviation of the ITI, flourishing scores, and allostatic load scores were performed, similar to D'Andrea-Penna et al. (2020). T-tests were also conducted on the N1 and P2 differences to assess their individual contributions. See Appendix for t-test results using N1 and P2 differences split by tapping measures.

Results

Descriptive Statistics

Vector Strength

VS was used to assess the ability to synchronize with an external rhythm, with a value of 1 indicating perfectly consistent tapping relative to the driving beat and 0 reflecting random tapping. The mean and median values for VS were 0.82 and 0.91, respectively, with a standard deviation of 0.19, indicating that most participants were competent at the tapping task. VS scores were not normally distributed (p = 0.001, Lilliefors's test statistic = 0.29) and were left skewed (-1.72 skewness).

Standard Deviation of ITI

Standard deviation of ITI was used to assess the tapping regularity, with a value of 0 seconds indicating perfect regularity. The mean and median values for standard deviation of ITI were both 0.03 seconds, with a standard deviation of 0.01 seconds, indicating that most participants were capable of tapping rhythmically. Standard deviation of the ITI was not normally distributed (p = 0.02, Lilliefors's test statistic = 0.15) and was right skewed (1.26 skewness).

Allostatic Load Scores

An allostatic load score was computed as a comprehensive measure of psychological and physical stress that reflected lifestyle choices alongside emotional health, with a score of 5 indicating maximum allostatic load and 0 reflecting no allostatic load. The mean and median values for the allostatic load score were 2.9 and 2.91, respectively, with a standard deviation of 0.4.

Secure Flourish Index

The secure flourish index was used as a standardized measure of allostatic load, with 0 indicating poorest wellbeing and 10 indicating maximal wellbeing. The mean and median values for the secure flourish measure were 6.6 and 6.5 respectively, with a standard deviation of 1.27.

N1-P2 to Deviants v. Standards

The N1-P2 magnitude to deviant beats (mean = 1.04, SD = 1.11) across subjects was larger than the N1-P2 to standard beats (mean = 0.14, SD = 0.25), as expected based on D'Andrea-Penna et al. (2020). This difference was statistically significant (paired one-tailed t-test, p = 2.1751e-06, t-stat = 4.95), indicating that unexpected beats elicit a larger N1-P2 than their expected counterparts (Figure 3.3).

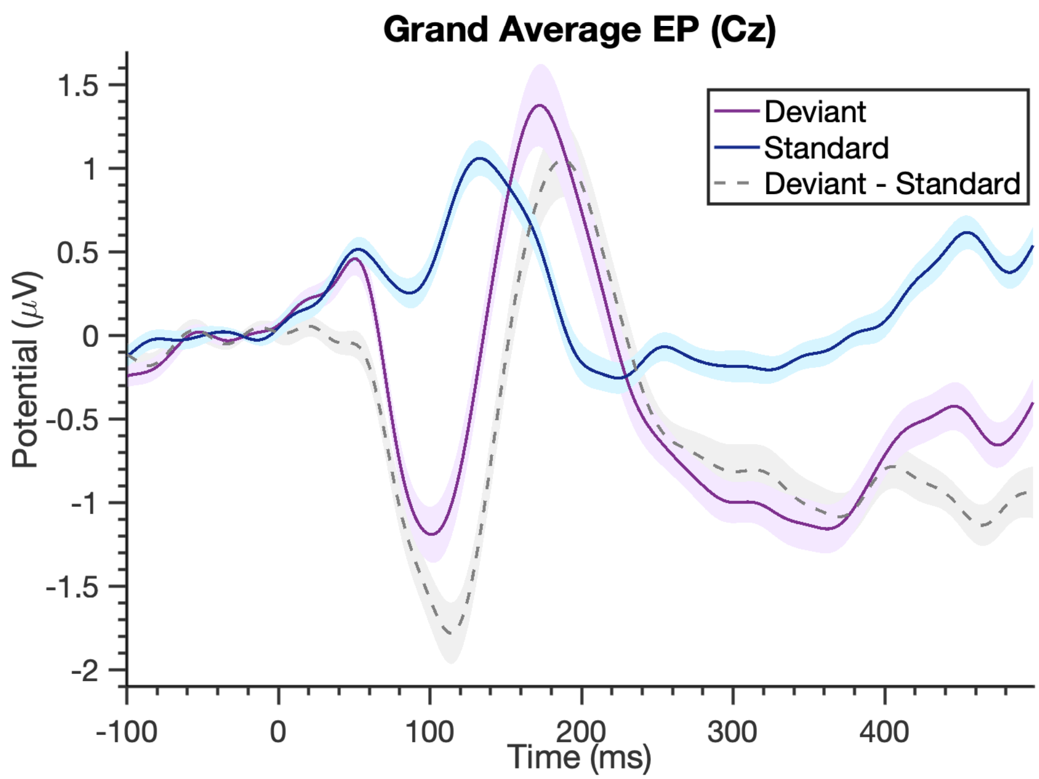


Figure 3.3: Grand average evoked potential is larger to deviant beats. Evoked potentials from Cz averaged across all 40 participants ("deviant" = unexpected beat in "long" condition, "standard" = expected beat in "short" condition). The N1P2 complex (a negative deflection around 100 ms post-stimulus followed by a positive deflection around 200 ms) is noticeably larger to deviant beats compared to standards, reflected in the gray dashed difference wave. The grand average N100 peak occurs at 88 ms and 102 ms for the standard and deviant conditions, respectively. The grand average P200 peak occurs at 132 ms to standards and 172 ms to deviants. The mean magnitudes +/- 50 ms around these peak times were taken for each subject, and the timing response index (TRI) was calculated as the N1P2 mean magnitude difference of deviant minus standard conditions.

Baseline Alpha Power

Among the 36 participants with identified alpha oscillations at the Cz electrode site, mean and median values for alpha power were 0.77 and 0.68 $\mu v^2/Hz$, respectively, with a standard deviation of 0.38 $\mu v^2/Hz$. Among the 37 participants with visible alpha oscillations identified from power spectral analysis at the Oz electrode site, mean and median values for alpha power were 0.9 and 0.74 $\mu v^2/Hz$, respectively, with a standard deviation of 0.57 $\mu v^2/Hz$.

Main Findings

Relationship between Resting-State Alpha Power & Allostatic Load Scores

The allostatic load score was significantly positively correlated with alpha power recorded over both Cz ($\rho = 0.37$, $p = 0.02$, N = 40) and Oz ($\rho = 0.54$, $p = 0.0006$, N = 38), indicating that lifestyle choices conferring allostatic load related to alpha oscillatory activity and thus cortical state (see Table 1 for data summary and Figure 3.4). To attempt to verify that this relationship was not an artifact arising from variability in cleaned resting-state data length or differences in eyes open or closed, we repeated the analysis using a partial correlation controlling for cleaned baseline length and number of eyeblinks detected in the raw data – the latter a proxy for eyes open or closed, assuming that those with eyes open would blink more. These partial correlations were similarly significant (Cz, $\rho = 0.4$, $p = 0.015$; Oz, $\rho = 0.55$, $p = 0.0006$). One-tailed t-tests comparing alpha power of participants with the 10 highest and lowest allostatic load scores for both Cz (t-stat = 1.76, $p = 0.048$, df = 18) and Oz (t-stat = 2.44, $p = 0.013$, df = 18) further validated these findings (Figure 3.5). Upon plotting the average power spectra for individuals with the 10 highest and lowest allostatic load scores, an apparent difference in beta oscillations was also observed in Oz. A follow-up correlation was indeed significant ($\rho = 0.45$, $p = 0.005$, N = 38) and held up when controlling for baseline length and number of eyeblinks ($\rho = 0.46$, $p = 0.006$). Accordingly, the effects of lifestyle and allostatic load on cortical resting state also involve changes in beta oscillatory activity.

In contrast, the secure flourish index was not significantly predictive of resting-state alpha power according to correlations (Cz, $\rho = -0.19$, $p = 0.23$; Oz, $\rho = -0.21$, $p = 0.21$) and t-tests (two-tailed, $p > 0.35$ for both Oz and Cz).

Table 3.1: Summary of main results. Significant correlations between spectral power and allostatic load scores suggest an influence of allostatic load on resting cortical state, such that those with greater allostatic load have more alpha and beta power (A). Correlations and t-tests between TRI and tapping measures (VS and standard deviation of the ITI) partially replicate D'Andrea-Penna et al. (2020): those with a larger TRI tend to perform better at the tapping task (B). * *indicates statistical significance at p <0.05.* T = t-statistic.

A)

Electrode Site	**Resting-State Measure**	**Allostatic Load Score**	**Secure Flourishing**	**TRI**
Cz (N = 40)	**Alpha**	$\rho = 0.37$, $p = 0.02$*	$\rho = -0.19$ $p = 0.23$	$\rho = -0.01$, $p = 0.96$
Oz (N = 38)	**Alpha**	$\rho = 0.54$, $p = 0.0006$*	$\rho = -0.21$, $p = 0.21$	$\rho = 0.17$, $p = 0.31$
	Beta	$\rho = 0.45$, p = 0.005*		

B)

	Allostatic Load Score		**Secure Flourishing**		**VS**		**SD of ITI**	
TRI	$\rho = 0.078$, $p = 0.63$	T = -0.55, $p = 0.29$	$\rho = -0.07$, $p = 0.65$	T = 0.92, $p = 0.18$	$\rho = 0.17$, $p = 0.29$	T = 2.02, $p = 0.029$*	$\rho = -0.48$, $p = 0.002$*	T = 2.2, $p = 0.02$*

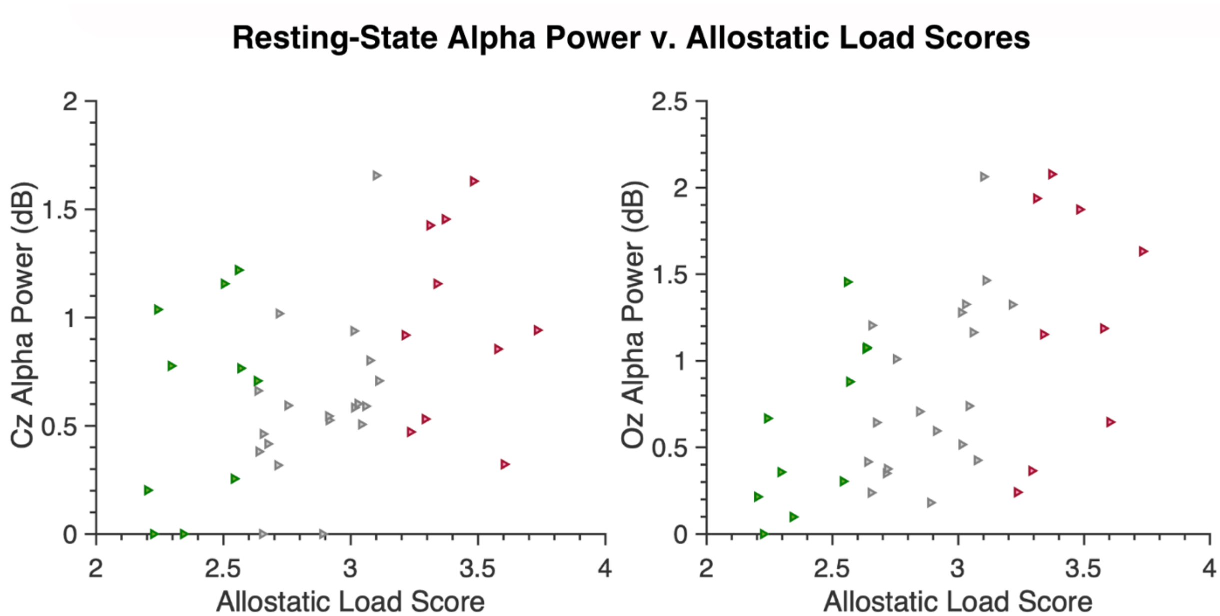


Figure 3.4: Allostatic load predicts resting-state alpha power. Scatter plot of peak alpha power and allostatic load scores indicates that individuals with greater allostatic load due to health risk behaviors and poor emotional wellbeing exhibit more alpha oscillatory activity in electrodes Cz ($\rho = 0.37$, $p = 0.02$) and Oz ($\rho = 0.54$, $p = 0.0006$) at rest. Red and green markers indicate participants with 10 highest and lowest allostatic load scores, respectively.

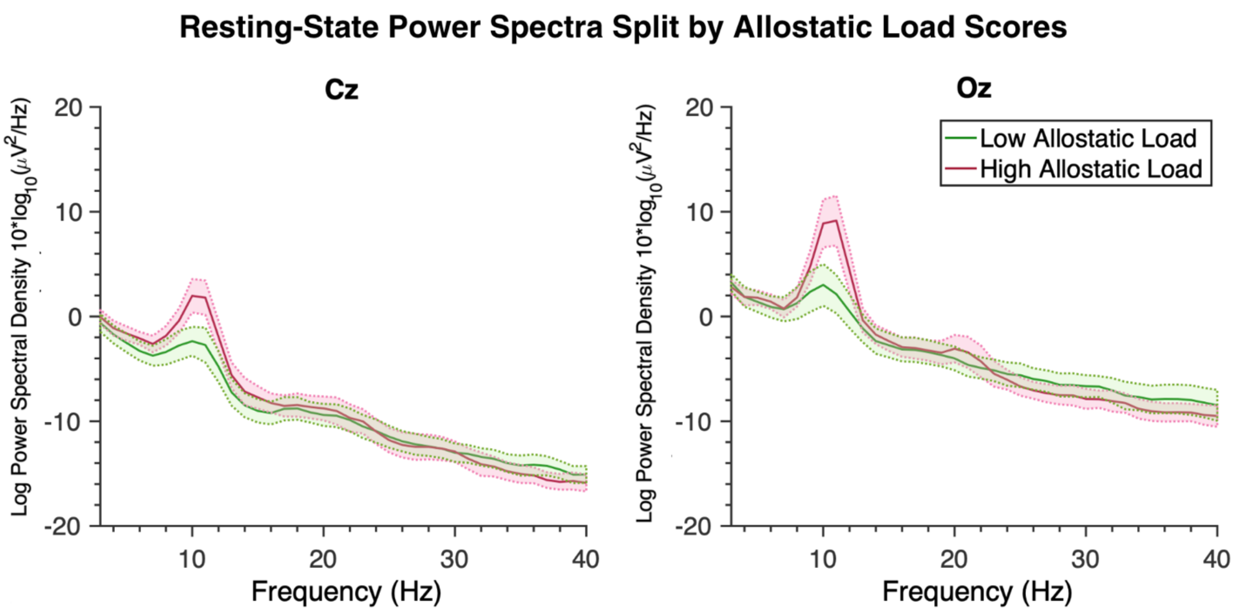


Figure 3.5: Individuals with highest allostatic load show larger alpha and beta oscillatory activity. Average power spectra of those with the 10 highest (red) and lowest (blue) allostatic load scores. Those with the highest allostatic load scores have more alpha oscillatory activity over Cz and Oz, as well as more beta oscillatory activity over Oz. Units of power plotted on y axis were log power spectral density, $10 * \log_{10} \frac{\mu v^2}{Hz}$.

Relationship between Spectral Activity & TRI

Neither correlation (Cz, $\rho = -0.01$, $p = 0.96$, N = 40; Oz, $\rho = 0.17$, $p = 0.31$, N = 38) nor t-test (Cz, t-stat = 0.29, $p = 0.77$, df = 18; Oz, t-stat = 1, $p = 0.33$, df = 18) showed a significant relationship between TRI and alpha power.

Relationship between TRI & Tapping

Analyses of the relationship between the TRI and tapping suggest that the ability to synchronize with an external beat predicts the brain response to temporal irregularities during passive listening only in individuals with very good or very poor synchronization. While the correlation between VS and TRI was not statistically significant ($\rho = 0.17$, $p = 0.29$, N = 40), a t-test comparing the TRI of participants with the 10 highest and lowest VS was (one-tailed, t-stat = 2.02, $p = 0.029$, df = 18). Thus, VS predicted TRI at the extremes of tapping performance, such that those with highest VS exhibited a much larger TRI than those with lowest VS.

On the other hand, tapping regularity was predictive of the brain response to unexpectedly timed beats both at the extremes and across the entire continuum of tapping regularity. The standard deviation of the ITI was significantly correlated with the TRI ($\rho = -0.48$, $p = 0.002$, N = 40), indicating that participants with a large TRI tended to be less variable tappers (Figure 3.6). A t-test comparing the TRI of participants with the 10 largest and smallest standard deviations of the ITI was similarly significant (one-tailed, t-stat = 2.2, $p = 0.022$, df = 18; Figure 3.7). These findings cumulatively suggest that TRI may be a marker of tapping regularity rather than SMS per se, at least in the population of young, healthy adults sampled for this study.

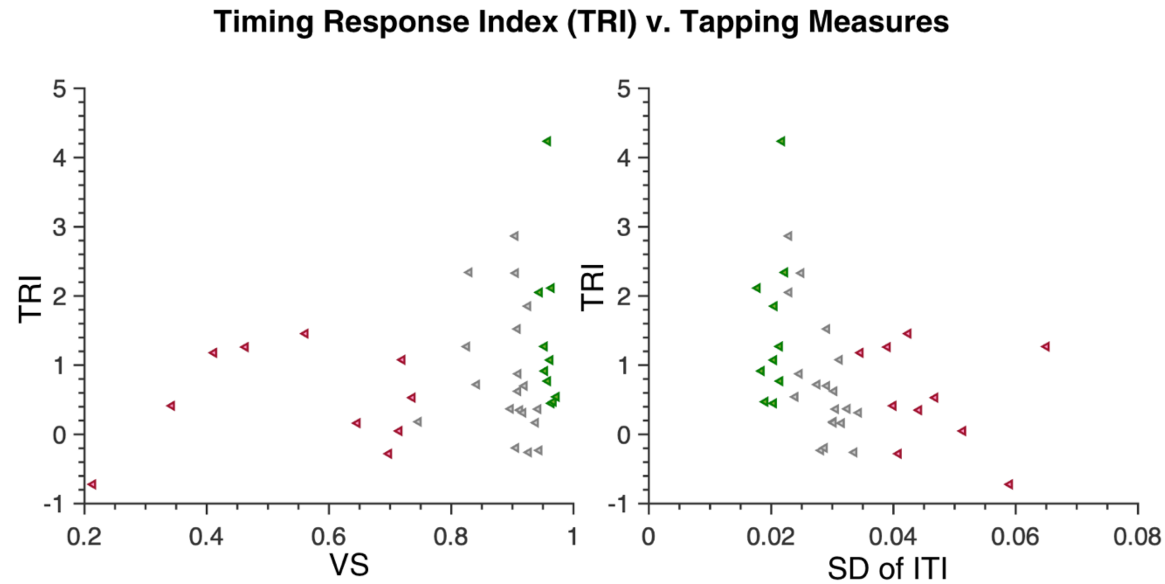


Figure 3.6: Brain responses to temporally unpredictable beats predict tapping measures. Scatter plots of VS and TRI (left) and standard deviation of the ITI and TRI (right). VS indicates ability to synchronize with an external rhythm, whereas standard deviation of the ITI indicates tapping variability. Red and green markers indicate participants with the 10 worst and best scores for each measure, respectively. Larger TRI reflects a larger brain response to deviant beats compared to standards. Individuals with a larger TRI tend to tap more regularly (ρ = -0.48, p = 0.002) and more synchronously with the external beat (ρ = 0.17, p = 0.29).

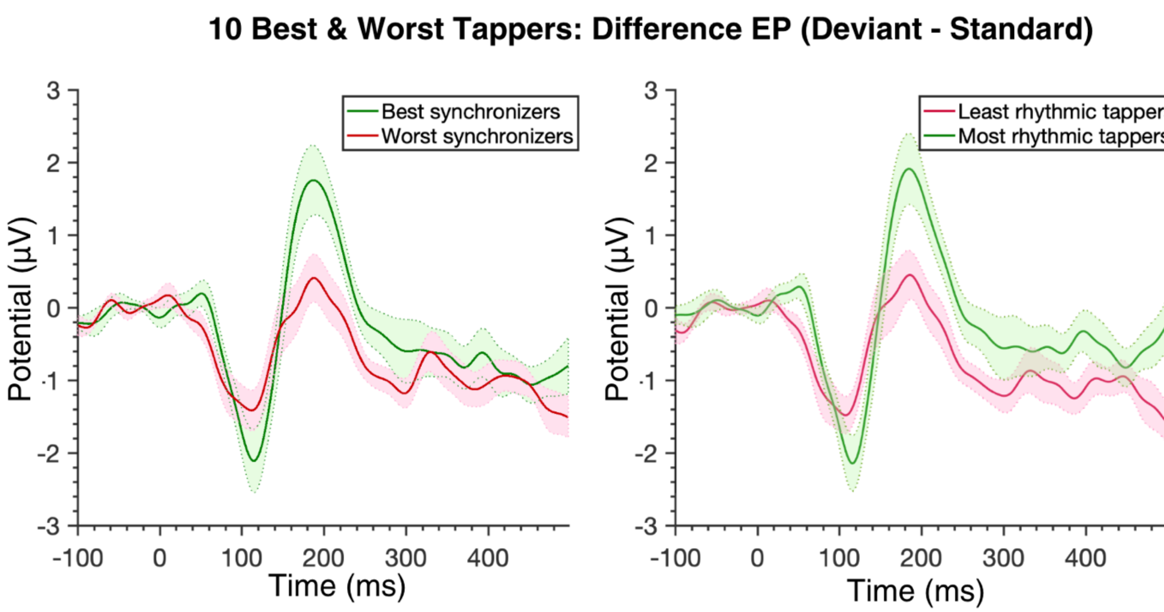


Figure 3.7: Best tappers show larger brain responses to temporally unpredictable beats. Difference wave (EP to deviant beat minus EP to standard, shading = SEM) of those with the 10 best (green) and worst (red) tappers, measured as Vector Strength (VS), or synchronization ability, on the left and as standard deviation of the ITI, or tapping rhythmicity, on the right. Those with the highest VS (the "best synchronizers") and lowest standard deviation of the ITI (the "most rhythmic tappers") tend to have a larger N1-P2 complex to deviant beats compared to those with the lowest VS and highest standard deviation of the ITI.

Relationship between TRI & Allostatic Load Score

Allostatic load scores were not significantly correlated with TRI ($\rho = 0.078$, $p = 0.63$), with the N1 difference magnitude ($\rho = -0.14$, $p = 0.4$), nor with the P2 difference magnitude ($\rho = -0.01$, $p = 0.95$). No t-tests were significant either (one-tailed, $p > 0.2$ for all).

Relationship between TRI & Secure Flourish Index

The secure flourish index was not significantly correlated with TRI ($\rho = -0.07$, $p = 0.65$), N1 difference magnitude ($\rho = -0.06$, $p = 0.72$), nor P2 difference magnitude ($\rho = -0.17$, $p = 0.29$). T-tests comparing the TRI (one-tailed, t-stat = 0.92, p = 0.18, df = 20), N1 difference (one-tailed, t-stat = 0.53, $p = 0.6$, df = 20), and P2 difference (one-tailed, t-stat = 1.45, $p = 0.08$, df = 20) of those with the 10 highest versus lowest flourishing scores were also not significant. Due to prior evidence suggesting an effect of socioeconomic status on the brain response to distracting stimuli (Stevens et al. 2009; Hampton Wray et al. 2017; Giuliano et al. 2018; Hao and Hu 2023), we examined whether the trending relationship between flourishing and the P2 difference derived from the financial and material stability dimension and found a significant correlation ($\rho = -0.32$, $p = 0.046$, N = 40). A t-test comparing those with the 10 highest and lowest financial and material stability scores was similarly significant (one-tailed, t-stat = 1.9, $p = 0.037$, df = 21), further suggesting that worrying about money and safety may exaggerate the brain response to unexpected stimuli.

Discussion

The present experiment aimed to examine the influence of allostatic load, measured as the culmination of health risk behaviors and emotional wellbeing, on resting cortical state and subsequent brain evoked potentials. We hypothesized that higher allostatic load would induce a hypervigilant cortical state reflected as lower resting-state alpha oscillatory power. In addition, we predicted that those with lower alpha at rest and higher allostatic load would exhibit a larger N1P2 response to temporally unexpected stimuli, thereby increasing the timing response index (TRI) in these individuals.

Our results indicate a significant effect of allostatic load on resting-state spectral power in both the alpha and beta bands. Higher allostatic load scores predicted greater alpha and beta power, the former observed in both central and occipital sites and the latter isolated to the occipital channel. Although the positive correlation between alpha and allostatic load contradicts both our initial hypothesis and common conceptions of alpha as a state of relaxed wakefulness, three potential explanations are supported by existing research. On the one hand, studies on depression suggest increased alpha oscillatory activity reflects internal, self-focused emotional processing (Schwartzmann et al. 2023). Accordingly, it is possible that higher alpha in those with more allostatic load reflects perseverative cognition (Brosschot et al. 2006). Alternatively, a separate body of evidence ties alpha to tonic alertness or vigilance (Knyazev and Slobodskaya 2003; Sadaghiani et al. 2010; Sadaghiani and Kleinschmidt 2016). Along these lines, increased alpha during tasks requiring sustained attention is associated with better performance (Makeig and Inlow 1993; Dockree et al. 2007; Braboszcz and Delorme 2011), and higher trait anxiety positively correlates with resting-state alpha power (Knyazev et al. 2004). Moreover, pharmacological manipulations of acetylcholine signaling (Osipova et al. 2003; Gianotti et al. 2008; Bauer et al. 2012) and reduced alpha activity found in individuals with Alzheimer's disease (Schreiter-Gasser et al. 1994; Gianotti et al. 2007) implicate the cholinergic system in alpha oscillations, further supporting this second interpretation (see Vakalopoulos 2014 for a comprehensive review). Cholinergic activity modulates cortical state, supporting an activated, aroused state conducive to attention, wakefulness, and better sensory encoding (Harris and Thiele 2011). Lastly, perhaps increased alpha in those with high allostatic load reflects greater fatigue, consistent with findings by Komarov et al. (2020). Nevertheless, were this the case, one would expect the sleep subscore of the allostatic load survey to primarily drive the correlation with alpha power; and we found no such relationship (see Supplemental Table 3.2).

Increased beta oscillatory activity accompanying higher allostatic load scores coheres with the role of beta in alertness and attention (Belyavin and Wright 1987; Wróbel 2000; Kamiński et al. 2012). Interestingly, the observed correlation with beta was seen specifically in the occipital electrode site. While reduced resting-state posterior beta has been reported in both Alzheimer's disease (de Haan et al. 2008) and ADHD (Hobbs et al. 2007), future research should further investigate this potential posterior beta enhancement due to chronic stress.

Resting-state alpha did not correlate with the secure flourish index, contrary to our hypothesis. Unlike the allostatic load survey, the flourishing questionnaire involved more subjective ratings about one's feelings and did not include more objective lifestyle-related questions. For instance, rather than probing about diet, sleep, or exercise habits, the flourishing questionnaire asked participants to rate their physical and mental health. Individual differences in subjective appraisal may affect such qualitative ratings, rendering them less accurate and, as a result, obscuring any relationship between flourishing and resting-state oscillations. Alternatively, it is possible that lifestyle choices overlooked in the flourishing questionnaire are simply an underappreciated contributor to overall wellbeing and resting cortical state.

Surprisingly, alpha power was also not associated with the TRI, suggesting that resting-state activity is not necessarily predictive of cortical state during sensory stimulation or of evoked potentials. Although previous studies have found a relationship between resting state activity and later event-related potentials (Ramos-Loyo et al. 2004; Lee et al. 2011; Li et al. 2015; Bojorges-

Valdez and Yanez-Suarez 2018), cortical state is dynamic and easily shifted by external stimulation (Tan et al. 2014; Deneux and Grinvald 2017). In this particular experiment, perhaps the onset of auditory stimuli increased cortical state activation compared to baseline silence, such that the two states shared little resemblance (Tan et al. 2014; Deneux and Grinvald 2017).

The relationship between the TRI and VS reported by D'Andrea-Penna et al. (2020) was partially replicated in our experiment. While the TRI was significantly larger in individuals with very high VS compared to those with very low VS, the correlation between TRI and VS did not reach significance, in contrast to our prior findings of a significant correlation (D'Andrea-Penna et al. 2020). However, the standard deviation of the ITI was significantly correlated with the TRI, such that more regular tappers had a larger TRI, which was also previously observed (see Appendix). The observed dissociation between these two behavioral timing measures, VS and standard deviation of the ITI, in relation to the TRI is surprising given the two variables are so highly correlated (see Appendix). These findings suggest that the TRI may be a more reliable marker of tapping regularity than VS per se.

One notable difference between the two studies is that the first was conducted prior to the COVID-19 pandemic, while the current study was conducted afterwards. The pandemic may have impacted the relationship between TRI and VS by exacerbating stress and anxiety while disrupting social interaction (Cianfarani and Pampanini 2023). Supporting such conjecture is the finding that increased loneliness interferes with interpersonal synchronization (Saporta et al. 2023), which is closely related to sensorimotor synchronization (SMS). In addition, altered temporal perception and SMS have been associated with confinement during the pandemic, suggesting an effect of stress and social isolation on tapping patterns (Droit-Volet et al. 2020; Gallego Hiroyasu et al. 2023). One might imagine that these factors impaired the ability to synchronize with external rhythms while preserving overall tapping regularity in those with proficient temporal processing, thereby disrupting the VS-TRI correlation but not the correlation between TRI and the standard deviation of the ITI. Moreover, adverse and lingering effects of the pandemic on youth mental health (Rogers et al. 2021; Horita et al. 2022; Gallego Hiroyasu et al. 2023) may also modulate the TRI, as research suggests stress can enhance neural processing of unexpected stimuli (Chang et al. 2015; Bangel et al. 2017; Zukerman et al. 2018; Ding et al. 2022; Ioakeimidis et al. 2023).

Counter to our hypothesis, we found no association between allostatic load and TRI in our undergraduate population. Since allostatic load erodes brain health slowly over time, examining its effects in college-aged students was likely not ideal (McEwen et al. 2015). Under these conditions, resting-state EEG may have been more sensitive at detecting such subtle changes than the TRI. Nevertheless, we did detect a positive correlation between the financial and material stability component of the flourishing questionnaire and the P2 difference – revealing that those who worry more about money and safety exhibit a larger P2 response to unexpected beats relative to standards. Low financial and material stability may index low socioeconomic status (SES); and consistent with our finding, low SES has been associated with larger brain response to irrelevant distractor stimuli (Stevens et al. 2009; Hampton Wray et al. 2017; Giuliano et al. 2018; Hao and Hu 2023). Such altered neural responsiveness can be adaptive in unsafe or uncertain environments, in which unexpected stimuli may more often than not constitute a threat.

While the present findings reveal interesting potential links between allostatic load and brain function, further research is needed to draw more definitive conclusions. Replicating this study with a larger sample size may improve the power and validity of the observed effects. Follow-up experiments should also incorporate more electrode coverage to assess frontal alpha asymmetry, a common marker of depression and mental illness. Additionally, separate resting-state sessions with explicit instructions for eyes open or closed will better isolate the effect of eye closure on alpha power in relation to the correlations reported here. Since reduced alpha amplitude suppression from eyes closed to open is associated with cognitive and attentional deficits (Bazanova and Vernon 2014), this differential could relate to allostatic load as well. As for the surveys used in this study, inquiring about loneliness and depression and incorporating more comprehensive, standardized mental health questionnaires may better elucidate participants' emotional wellbeing. Lastly, including physiological measures, such as respiration and heart rate, heart-rate variability, and skin conductance would offer more objective markers of stress and allostatic load.

Conclusion

Health risk behaviors and poor mental health confer a cumulative stress burden, or *allostatic load*, that can alter brain structure and function over time. We found such changes manifest most prominently in the resting-state spectral activity of young adults, in which higher allostatic load correlated with greater alpha and beta oscillatory power at rest. Increased power in these frequency bands likely reflects heightened arousal or vigilance under stress, which provides an adaptive advantage in potentially unsafe environments.

Acknowledgements

Chapter 3 contains unpublished material co-authored with Chiba, Andrea A; Khalil, Alex K; Iversen, JR; Minces, VH. The dissertation author was the primary investigator and author of this paper.

Appendix

Questionnaires

Flourishing Measure
From VanderWeele (2017)

1. Overall, how satisfied are you with life as a whole these days?
   0 = Not Satisfied at All, 10 = Completely Satisfied
2. In general, how happy or unhappy do you usually feel?
   0 = Extremely Unhappy, 10 = Extremely Happy
3. In general, how would you rate your physical health?
   0 = Poor, 10 = Excellent
4. How would you rate your overall mental health?
   0 = Poor, 10 = Excellent
5. Overall, to what extent do you feel the things you do in your life are worthwhile?
   0 = Not at All Worthwhile, 10 = Completely Worthwhile
6. I understand my purpose in life.
   0 = Strongly Disagree, 10 = Strongly Agree
7. I always act to promote good in all circumstances, even in difficult and challenging situations.
   0 = Not True of Me, 10 = Completely True of Me
8. I am always able to give up some happiness now for greater happiness later.
   0 = Not True of Me, 10 = Completely True of Me
9. I am content with my friendships and relationships.
   0 = Strongly Disagree, 10 = Strongly Agree
10. My relationships are as satisfying as I would want them to be.
    0 = Strongly Disagree, 10 = Strongly Agree
11. How often do you worry about being able to meet normal monthly living expenses?
    0 = Worry All of the Time, 10 = Do Not Ever Worry
12. How often do you worry about safety, food, or housing?
    0 = Worry All of the Time, 10 = Do Not Ever Worry

Allostatic Load Survey

Sleep Subscore Questions

On average…
How much sleep do you get each night?
Response options: under 4 hours, 4-6 hours, 7-9 hours, 9+ hours
How rested do you feel upon waking?
Response options: Not at all (1) to Fully (5)
How hard is it for you to get out of bed in the morning?
Response options: Very hard (1) to Very easy (5)
How often do you have trouble falling asleep or staying asleep?
Response options: Less than once a week, 1-2 times/week, 3-5 times/week, 6+ times/week

Nutrition Subscore Questions

On average…

How many servings of fruits and vegetables do you consume daily?

Response options: None, 1-2 servings, 3-4 servings, 5-6 servings, 7 or more servings

How often do you cook your own food?

Response options: Never (1) to Always (5)

How often do you consider the nutritional content of your food?

Response options: Never (1) to Always (5)

How quickly do you eat your food?

Response options: Very quickly (1) to Very slowly (5)

How often do you eat out?

Response options: Less than once a week, 1-2 times/week, 3-5 times/week, 6+ times/week

How often do you consume fast food?

Response options: Less than once a week, 1-2 times/week, 3-5 times/week, 6+ times/week

How often do you drink sweetened beverages?

Response options: Less than once a week, 1-2 times/week, 3-5 times/week, 6+ times/week

How often do you consume ultra-processed foods?

Examples include packaged chips, candy, bars, instant noodles, etc.

Response options: Less than once a week, 1-2 times/week, 3-5 times/week, 6+ times/week

How often do you prioritize whole foods?

Response options: Never (1) to Always (5)

Exercise Subscore Questions

On average…

How often do you engage in regular aerobic activity each week?

Aerobic activity, or "cardio," includes any exercise that raises your heart rate & breathing rate for 10+ minutes.

Response options: Never, less than once a week, 1-2 times/week, 3-4 times/week, 5 or more times/week

How often do you engage in team sports each week?

Response options: Never, less than once a week, 1-2 times/week, 3-4 times/week, 5 or more times/week

How often do you resistance train or lift weights each week?

Response options: Never, less than once a week, 1-2 times/week, 3-4 times/week, 5 or more times/week

How often do you practice yoga each week?

Response options: Never, less than once a week, 1-2 times/week, 3-4 times/week, 5 or more times/week

How often do you practice pilates each week?

Response options: Never, less than once a week, 1-2 times/week, 3-4 times/week, 5 or more times/week

How physically active are you throughout the day?

Response options: Sitting all day (1) to Constantly on the move (2)

Technology Use Subscore Questions

On average…

How often do you use your phone per day?
If possible, check usage statistics on your phone.
Response options: More than 6 hours, 4-6 hours, 2-4 hours, 1-2 hours, less than 1 hour
How often do you visit social media apps & sites daily?
Response options: More than 5 times a day, 3-5 times a day, 1-2 times a day, every few days, rarely or never
How often do you watch/stream shows or videos per week?
Response options: More than 5 times a week, 3-5 times a week, 1-2 times a week, once a week or less, rarely or never
How often do you use screens (phone, TV, computer) within 2 hours of going to sleep?
Response options: Never (1) to Always (5)

Emotional Wellbeing Subscore Questions

On average…
How often do you feel overwhelmed?
Response options: Never (1) to Always (5)
How often do you feel relaxed?
Response options: Never (1) to Always (5)
How often do you feel stressed?
Response options: Never (1) to Always (5)
How often do you feel carefree?
Response options: Never (1) to Always (5)
How often do you feel anxious?
Response options: Never (1) to Always (5)
How often do you feel happy?
Response options: Never (1) to Always (5)
How often do you feel confident in your ability to manage life?
Response options: Never (1) to Always (5)
How often do you find yourself stressed about things you can't control?
Response options: Never (1) to Always (5)
How often do you find yourself stressed about things you can control?
Response options: Never (1) to Always (5)

Supplemental Tables

Supplemental Table 3.1: Resting-state spectral correlations using 60 seconds of data per subject. When excluding participants with less than 60 s of data and repeating the spectral FOOOF analysis with 60s of resting-state data from each participant, alpha in both Cz and Oz are still significantly correlated with allostatic load scores but beta is not. ** indicates statistical significance at $p < 0.05$*

	Cz Alpha Power (N = 38)	**Oz Alpha Power (N = 36)**	**Cz Beta Power (N = 38)**	**Oz Beta Power (N = 36)**
Allostatic Load Score	ρ = 0.34, *p* = 0.036*	ρ = 0.68, *p* = 0.000006*	ρ = 0.01, *p* = 0.95	ρ = 0.19, *p* = 0.26
Secure Flourish Index	ρ = -0.28, *p* = 0.09	ρ = -0.15, *p* = 0.38	ρ = 0.12, *p* = 0.45	ρ = 0.03, *p* = 0.87
TRI	ρ = 0.01, *p* = 0.97	ρ = 0.15, *p* = 0.39	ρ = 0.02, *p* = 0.89	ρ = 0.32, *p* = 0.31

Supplemental Table 3.2: Relationship between allostatic load score subsections and alpha power. The exercise subsection was significantly correlated with alpha oscillatory power in both Cz and Oz, while the sleep subsection was significantly correlated with alpha power in Oz. *N = 40 for all correlations with Cz alpha; N = 38 for all correlations with Oz alpha.* ** indicates statistical significance at $p < 0.05$*

Subsection *(higher score = more allostatic load)*	**Correlation w/ Cz Alpha**	**Correlation w/ Oz Alpha**
Sleep	ρ = 0.26, *p* = 0.1	ρ = 0.35, *p* = 0.03*
Nutrition	ρ = 0.12, *p* = 0.47	ρ = 0.2, *p* = 0.24
Exercise	ρ = 0.37, *p* = 0.02*	ρ = 0.45, *p* = 0.0047*
Technology Use	ρ = 0.2, *p* = 0.23	ρ = 0.32, *p* = 0.05
Emotional Wellbeing	ρ = 0.1, *p* = 0.55	ρ = 0.28, *p* = 0.09

Supplemental Table 3.3: Resting-state spectral correlations excluding subjects with no identified alpha or beta peak. When excluding participants for whom FOOOF identified no alpha or beta peak (instead of assigning them a peak of zero), alpha and beta in Oz still significantly correlate with allostatic load. Cz alpha, while not significantly correlated with allostatic load scores in this case, shows a similar trend. * *indicates statistical significance at $p < 0.05$*

	Cz Alpha Power (N = 36)	**Oz Alpha Power (N = 37)**	**Cz Beta Power (N = 31)**	**Oz Beta Power (N = 32)**
Allostatic Load Score	ρ = 0.28, *p* = 0.11	ρ = 0.5, *p* = 0.002*	ρ = 0.14, *p* = 0.46	ρ = 0.43, *p* = 0.02*
Secure Flourish Index	ρ = -0.18, *p* = 0.3	ρ = -0.14, *p* = 0.41	ρ = -0.02, *p* = 0.93	ρ = -0.31, *p* = 0.08
TRI	ρ = -0.10, *p* = 0.55	ρ = 0.24, *p* = 0.16	ρ = 0.23, *p* = 0.21	ρ = 0.19, *p* = 0.31

Supplemental Table 3.4: Relationship among allostatic load score subsections. Exercise scores were significantly positively correlated with sleep scores, such that individuals with higher levels of physical activity tended to have better sleep. Exercise was also associated with better emotional wellbeing (though not statistically significant, $p = 0.06$). *N = 40 for all, * indicate statistical significance at $p > 0.05$*

	Nutrition	**Exercise**	**Technology Use**	**Emotional Wellbeing**
Sleep	ρ = 0.04, *p* = 0.81	ρ = 0.33, *p* = 0.04*	ρ = 0.06, *p* = 0.7	ρ = 0.26, *p* = 0.11
Nutrition		ρ = 0.21, *p* = 0.19	ρ = 0.21, *p* = 0.2	ρ = 0.08, *p* = 0.61
Exercise			ρ = 0.02, *p* = 0.91	ρ = 0.3, *p* = 0.06
Technology Use				ρ = 0.17, *p* = 0.28

Supplemental Table 3.5: Relationship between allostatic load score subsections and beta power. The technology use and emotional wellbeing subsections were significantly correlated with beta oscillatory power in Oz. *N = 38 for all correlations. * indicates statistical significance at p < 0.05*

Subsection *(higher score = more allostatic load)*	**Correlation w/ Oz Beta**
Sleep	ρ = 0.15, p = 0.38,
Nutrition	ρ = 0.08, p = 0.62
Exercise	ρ = 0.22, p = 0.1869
Technology Use	ρ = 0.37, p = 0.02*
Emotional Wellbeing	ρ = 0.46, p = 0.004*

Supplemental Table 3.6: Relationship between allostatic load and tapping. Neither allostatic load scores nor the secure flourishing index was significantly correlated with VS or standard deviation of the ITI. *N = 40 for all.*

	VS	**Standard Deviation of ITI**
Allostatic Load Score	ρ = 0.21, *p* = 0.19	ρ = -0.1, *p* = 0.68
Secure Flourishing Index	ρ = -0.26, *p* = 0.11	ρ = 0.17, *p* = 0.28

Supplemental Table 3.7: Relationship between musical experience and tapping. Musical experience was significantly correlated with both VS and standard deviation of the ITI, such that those with musical experience were both more regular and more synchronous tappers. *N = 40 for all. * indicates statistical significance at p < 0.05*

	VS	**Standard Deviation of ITI**
Musical experience (y/n)	ρ = 0.43, *p* = 0.005*	ρ = -0.36, *p* = 0.02*

Supplemental Table 3.8: Correlational analyses using different window sizes for the TRI calculation. Recalculating the TRI using mean magnitudes of shorter windows of 20-ms, 40-ms, and 60-ms around the grand average N1 and P2 peak times yielded similar results to the original analyses. SD of the ITI was still found to significantly correlate with the TRI, while a nonsignificant trend was observed between VS and TRI. Neither allostatic load measures were correlated with TRI, regardless of window size. *N = 40 for all. * indicates statistical significance at p < 0.05*

	TRI w/ 20-ms window	**TRI w/ 40-ms window**	**TRI w/ 60-ms window**
VS	$\rho = 0.15$, $p = 0.34$	$\rho = 0.17$, $p = 0.29$	$\rho = 0.15$, $p = 0.35$
SD of ITI	$\rho = -0.44$, $p = 0.005$*	$\rho = -0.46$, $p = 0.003$*	$\rho = -0.45$, $p = 0.004$*
Allostatic Load Score	$\rho = 0.12$, $p = 0.41$	$\rho = 0.15$, $p = 0.37$	$\rho = 0.13$, $p = 0.41$
Secure Flourishing Index	$\rho = 0.05$, $p = 0.75$	$\rho = 0.01$, $p = 0.94$	$\rho = -0.02$, $p = 0.91$

Other Supplemental Analyses

Baseline Aperiodic Activity

At electrode site Cz, mean and median aperiodic slope exponent values were both 1.5, with a standard deviation of 0.27. At electrode site Oz, the mean and median values were 1.22 and 1.32, respectively, with a standard deviation of 0.42.

Correlation between VS & Standard Deviation of the ITI

VS was significantly correlated with standard deviation of the ITI ($\rho = -0.7675$, $p = 1.3283e\text{-}07$, N = 40).

Correlation between Beta Power in Cz & Allostatic Load Scores

Beta power in Cz was not significantly correlated with allostatic load scores ($\rho = 0.11$, $p = 0.5$, N = 40).

Relationship between Aperiodic Spectral Activity & TRI

Upon plotting the average power spectra for Oz comparing participants with the 10 highest and lowest TRI, we observed the aperiodic slope was steeper in those with higher TRI. A follow-up correlation between the aperiodic exponent in Oz and TRI was, in fact, significant ($\rho = 0.41$, $p = 0.01$, N = 38). This correlation also held up when controlling for resting-state data length and number of blinks ($\rho = 0.42$, p = 0.01, N = 38); and was similarly significant in a t-test (one-tailed, t-stat = 1.81, $p = 0.04$, df = 18). Aperiodic activity in Cz, however, was not significantly correlated with the TRI ($\rho = 0.17$, $p = 0.29$, N = 40).

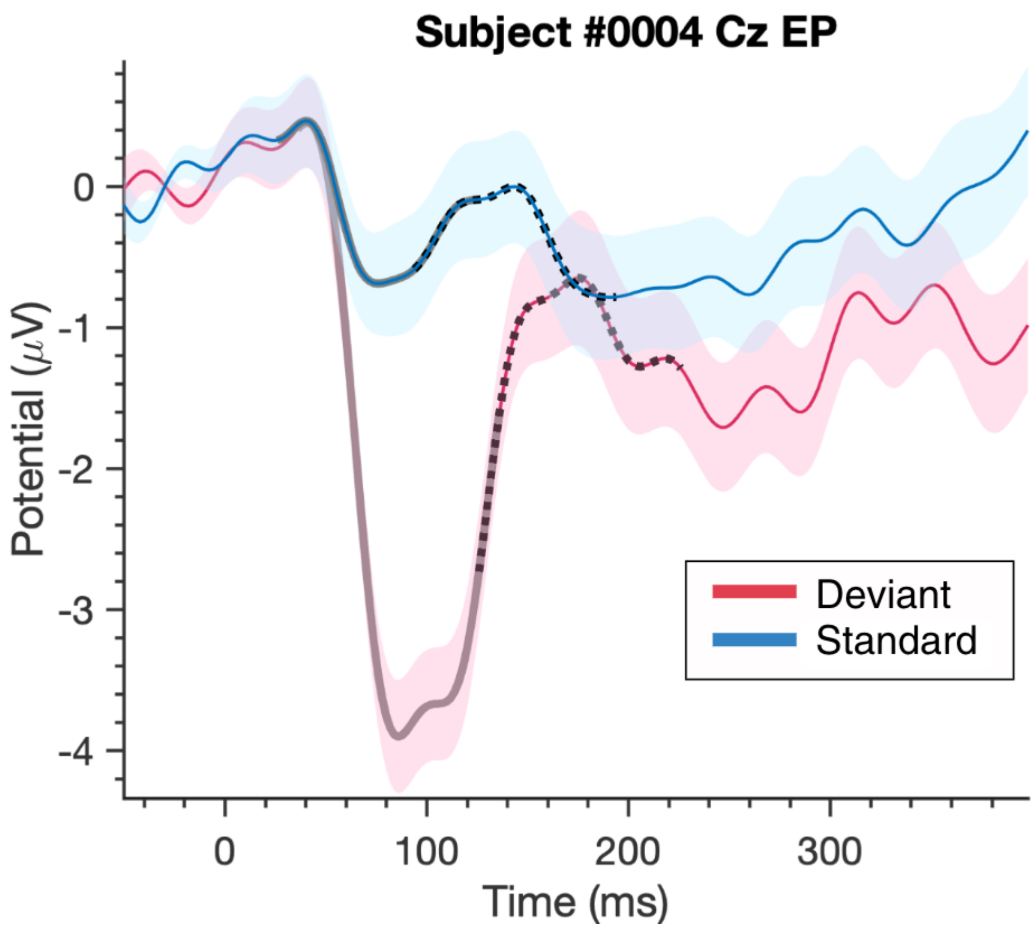
Relationship between N1/P2 Difference & Tapping

Repeating the correlational analyses with the N1 and P2 difference magnitudes separately found no relationship between the N1 difference alone and VS ($p > 0.4$ for both correlation and one-tailed t-test) or standard deviation of the ITI ($p > 0.3$ for both tests). The P2 difference magnitude, on the other hand, demonstrated a significant relationship with standard deviation of the ITI (correlation, $\rho = -0.38$ and 0.015, N = 40; one-tailed t-test, t-stat = 2.1, $p = 0.027$, df = 18) but was not significantly correlated with VS ($\rho = 0.21$, $p = 0.2$). Nonetheless, a one-tailed t-test comparing P2 difference magnitudes of participants with the 10 best and worst VS scores was significant (t-stat = 1.99, $p = 0.03$, df = 18). Consequently, the P2 difference appears to be the primary – though likely not the only – contributor to the predictive value of the TRI.

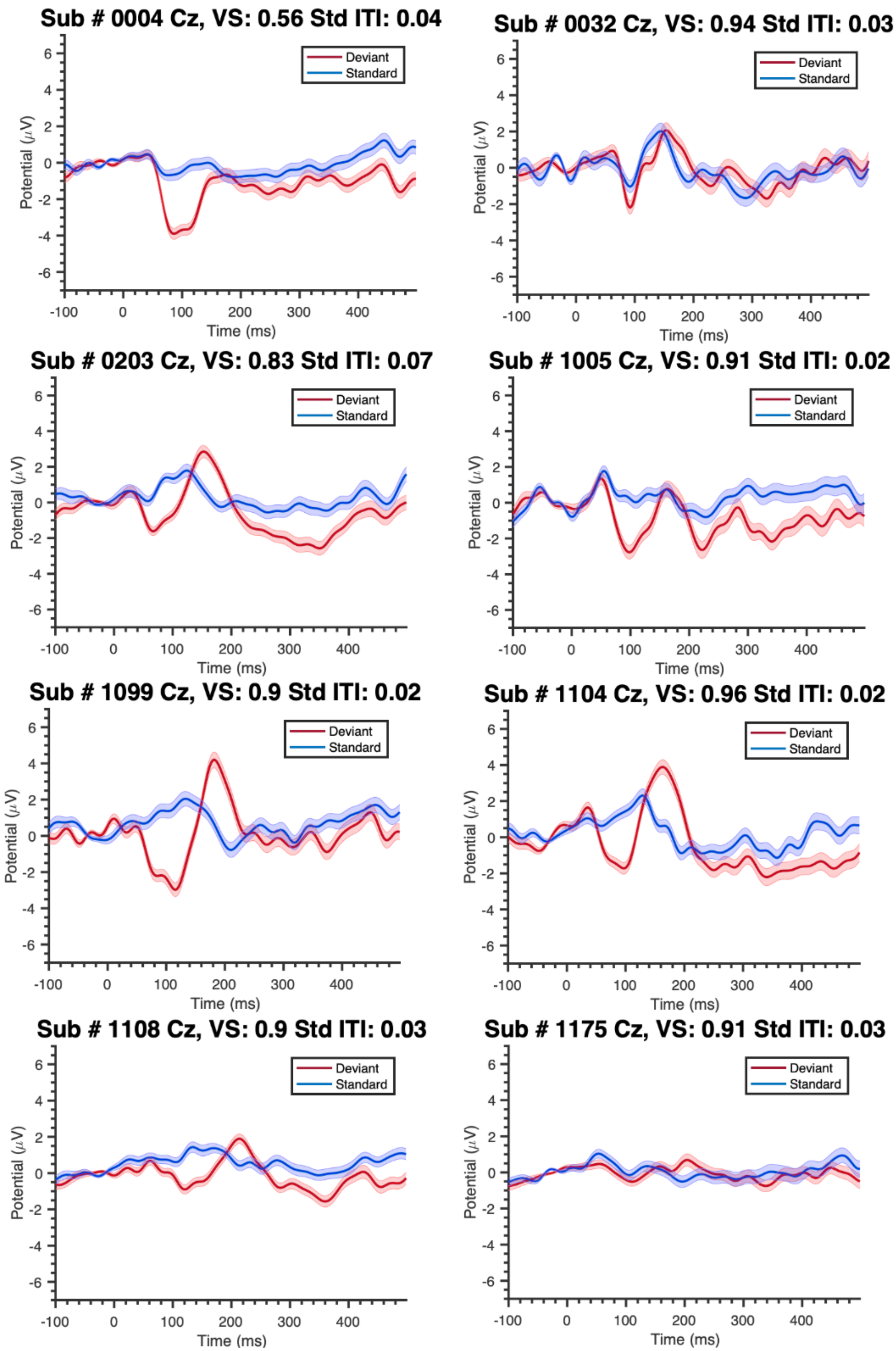
Relationship between TRI & Standard Deviation of the ITI in Prior Experiment

The TRI significantly correlated with the standard deviation of the ITI in our prior experiment (D'Andrea-Penna et al. 2020) as well ($\rho = -0.45$, $p = 0.0077$, N = 40). A one-tailed t-test of the TRI of those with the 10 highest and lowest standard deviations of the ITI was also significant (t-stat = 2.6, $p = 0.009$, df = 18).

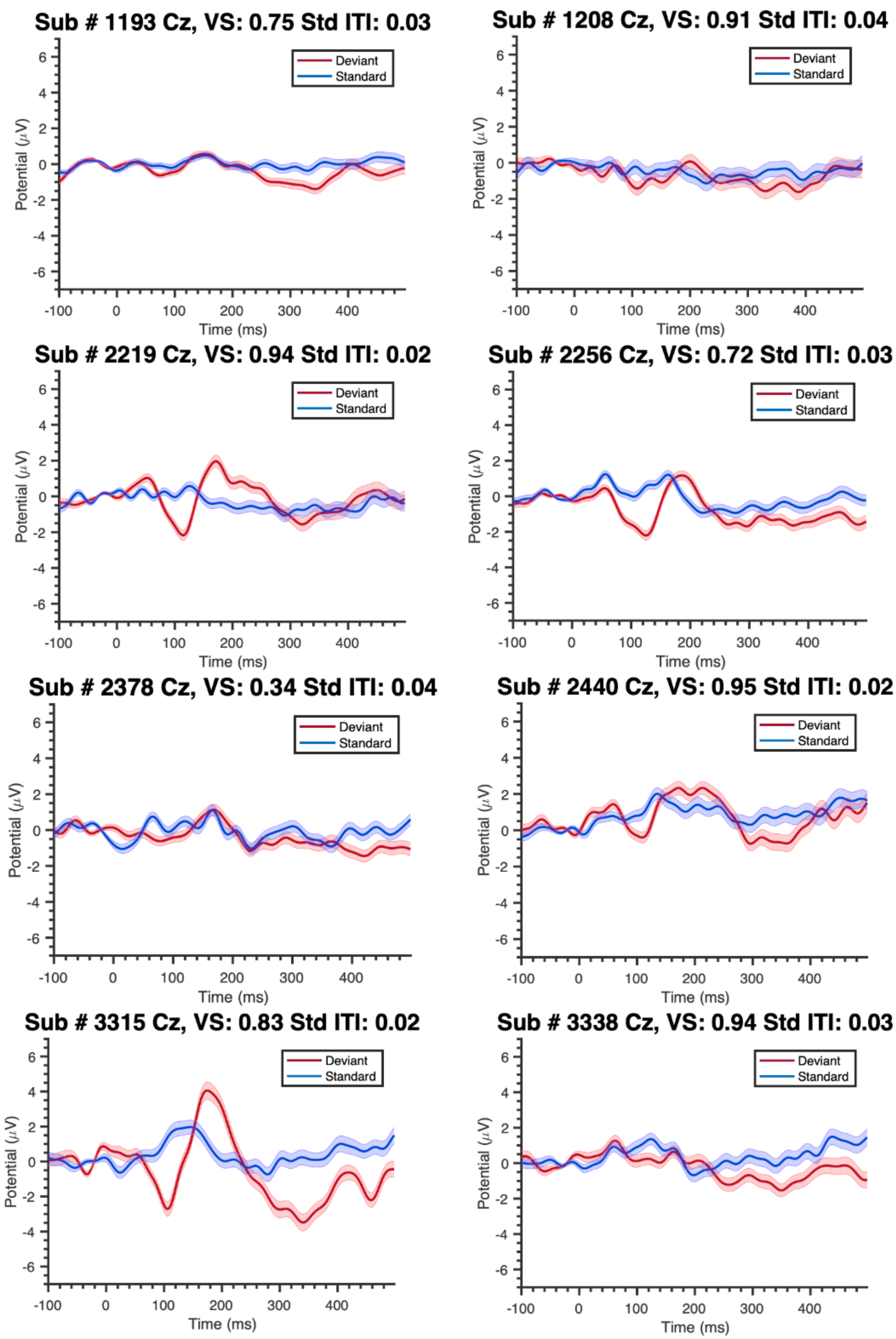
Supplemental Figures



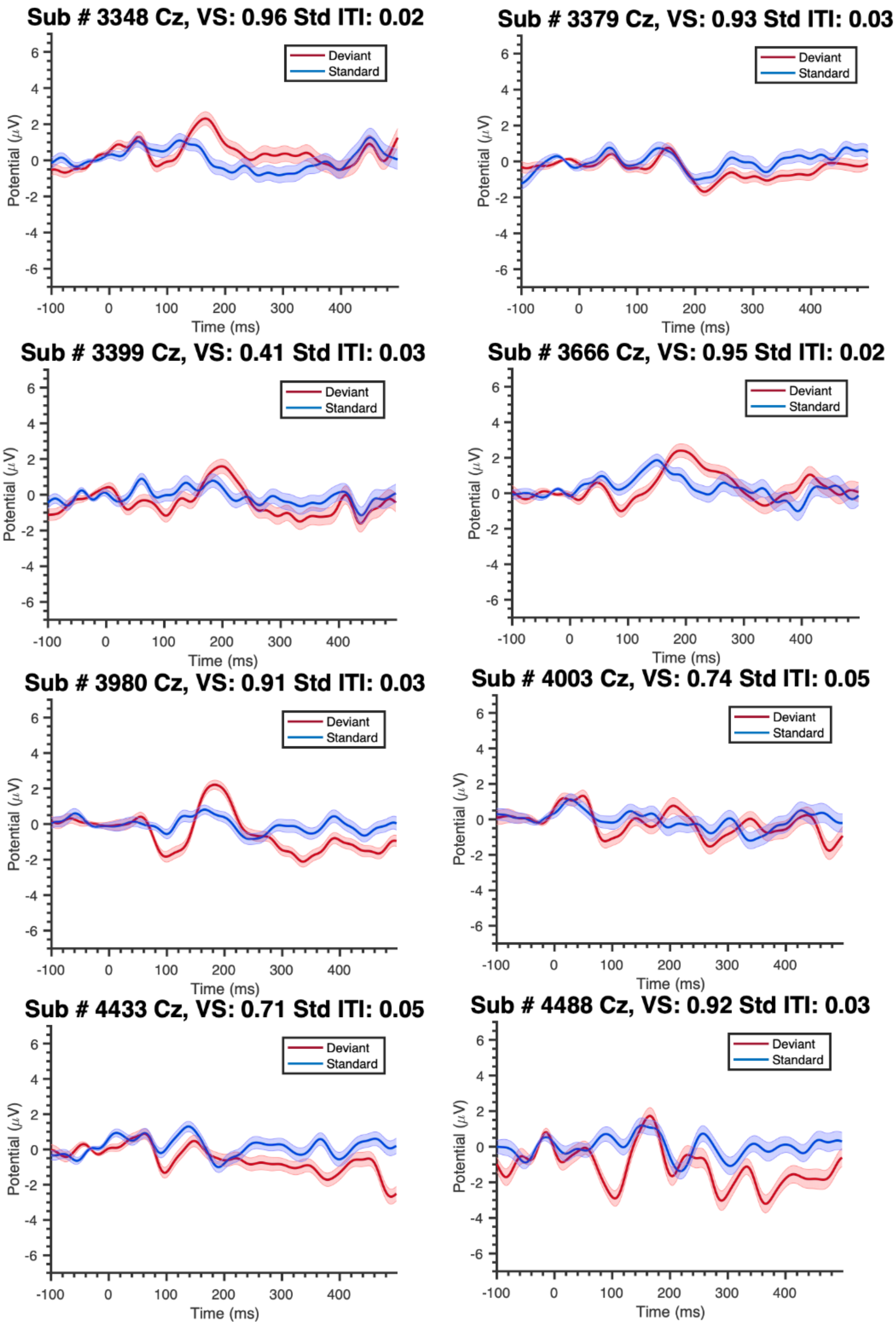
Supplemental Figure 3.1: Example of timing response index (TRI) identification in a single subject. TRI was calculated as the N1P2 mean magnitude differential between deviant (*red*) and standard (*blue*) evoked potentials (EPs). Mean amplitude value for the standard N1 was taken between 38 and 138 ms and for standard P2 was taken between 82 and 182 ms; mean amplitude value for deviant N1 was taken between 52 and 152 ms and for deviant P2 was taken between 122 and 222 ms (see *gray solid lines for N1 windows and black dotted lines for P2 windows*). These windows were based on the grand average EP for each condition.



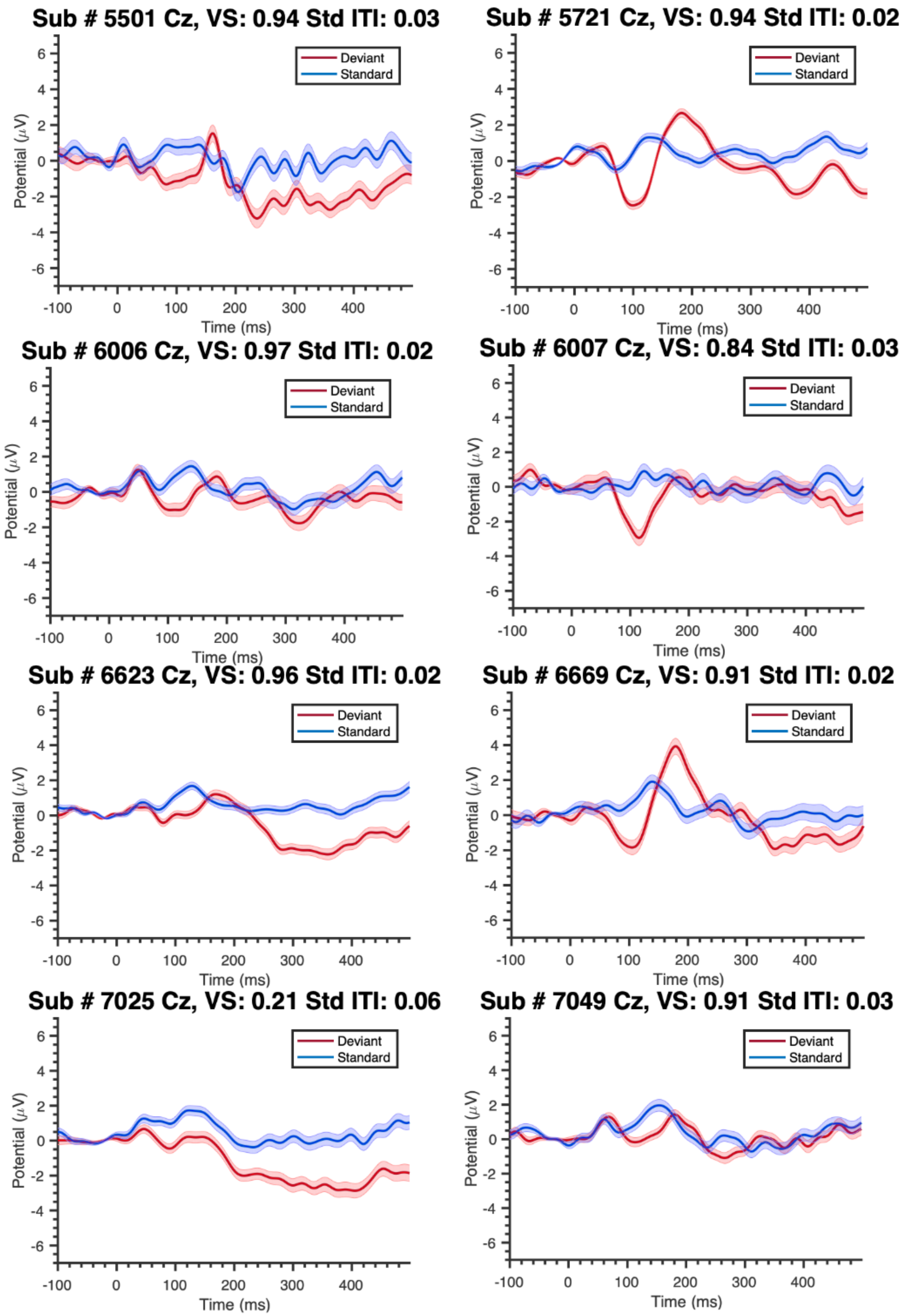
Supplemental Figure 3.2: Single-subject passive listening evoked potentials.



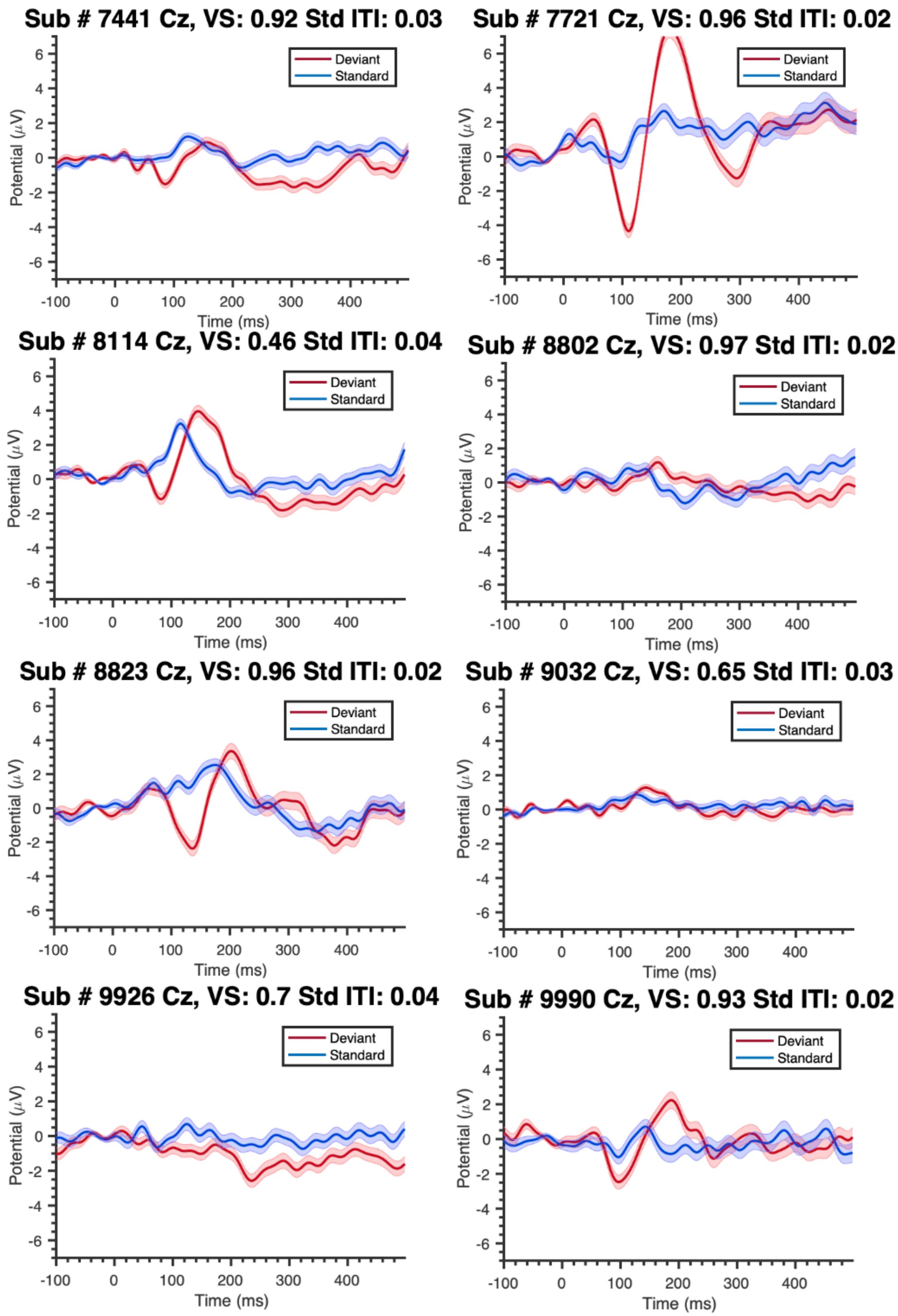
Supplemental Figure 3.2: Single-subject passive listening evoked potentials, Continued



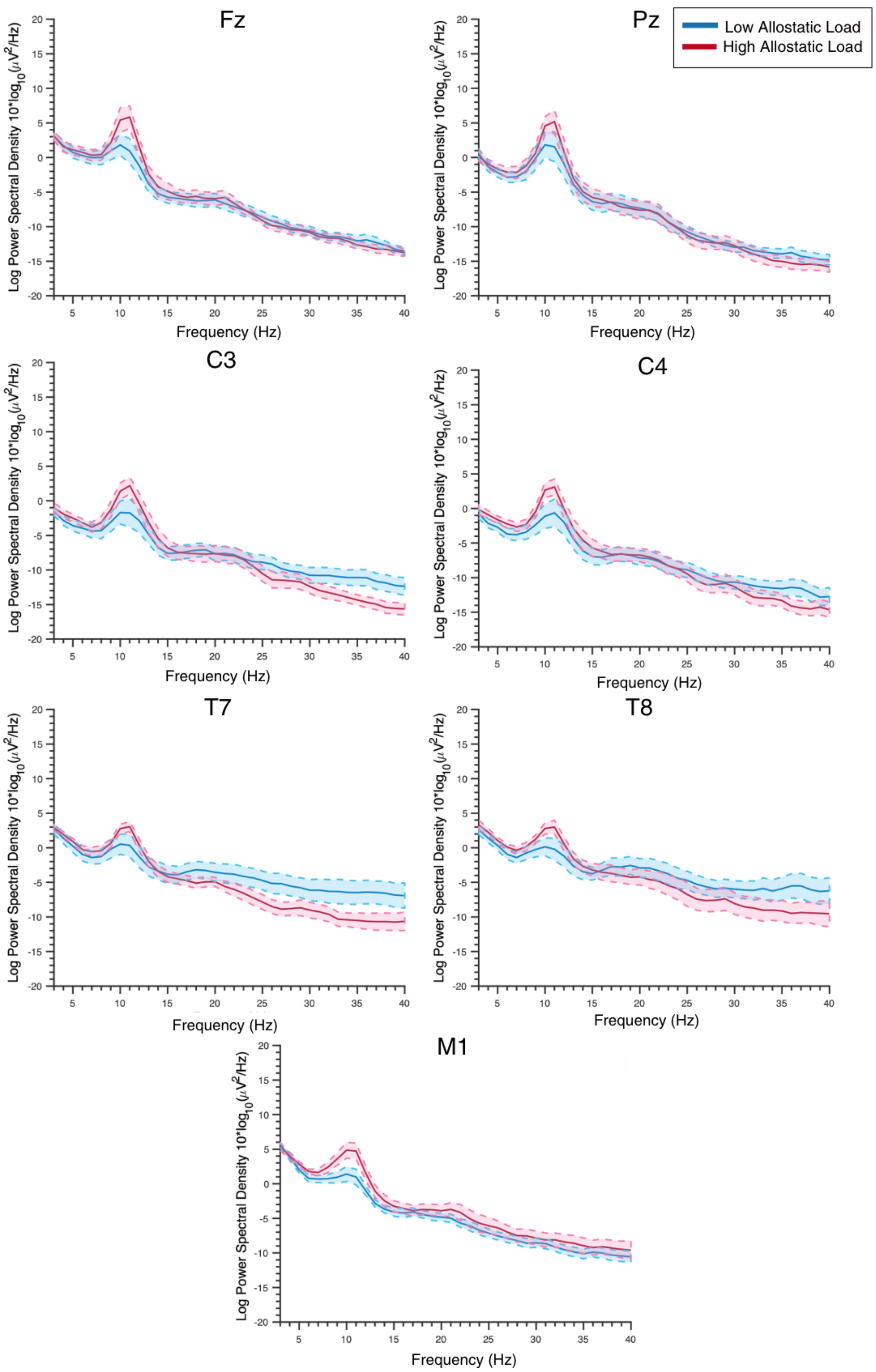
Supplemental Figure 3.2: Single-subject passive listening evoked potentials, Continued



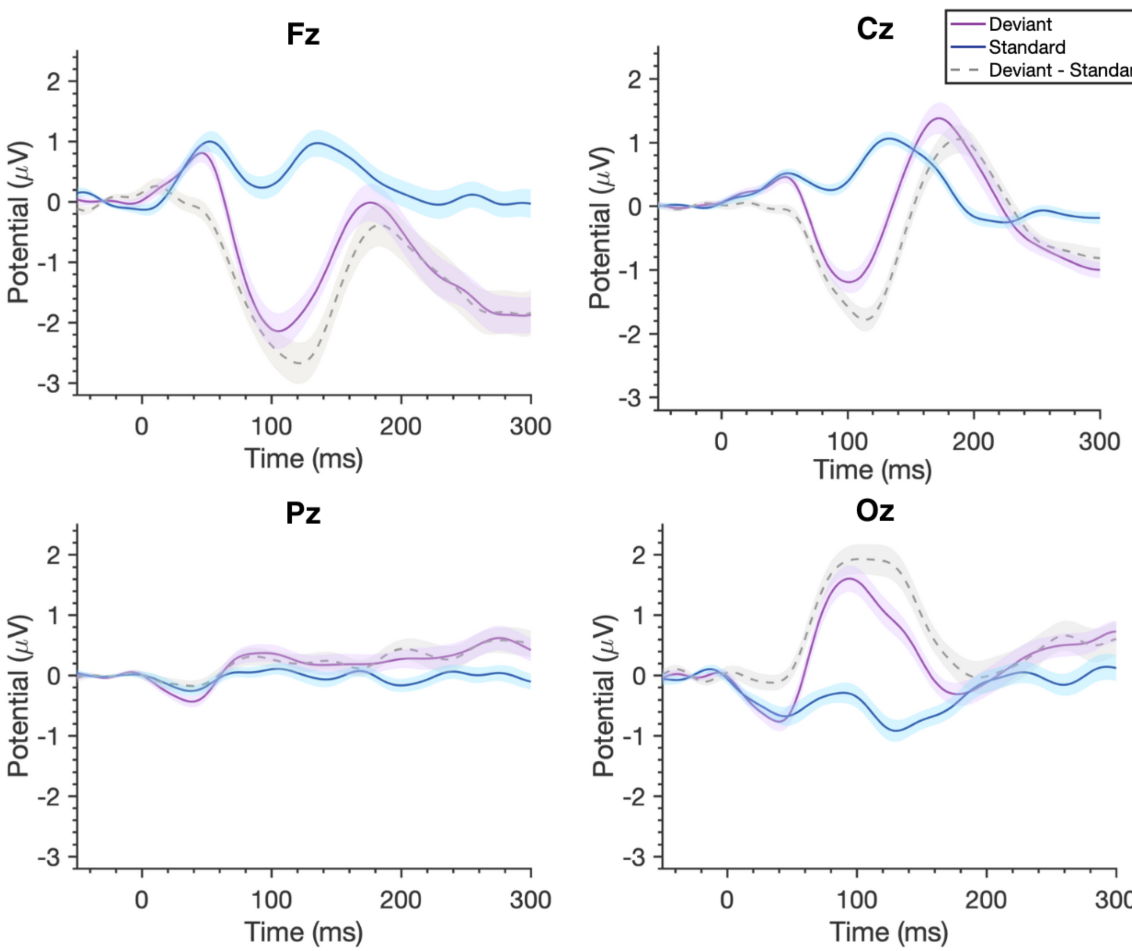
Supplemental Figure 3.2: Single-subject passive listening evoked potentials, Continued



Supplemental Figure 3.2: Single-subject passive listening evoked potentials, Continued



Supplemental Figure 3.3: Resting state power spectra for other electrode sites. Comparing resting-state average spectra of those with the 10 lowest and highest allostatic load scores. There is an overall trend for higher alpha power in those with highest allostatic load scores across all electrode sites. Units of power plotted on y axis were log power spectral density, $10 * \log_{10} \frac{\mu v^2}{Hz}$.



Supplemental Figure 3.4: Grand average evoked potentials across midline electrodes. The MMN-like difference wave (dashed gray line) prominent in anterior channels is largest at Fz, with a slightly later peak latency compared to Cz (122 ms v. 114 ms). Since these latencies overlap with time windows used for calculating the TRI, we also conducted a more traditional MMN analysis, taking the mean magnitude of the difference wave between 102 and 142 ms in Fz and between 94 and 134 ms in Cz, guided by these grand averages. The Fz MMN was not significantly correlated with the TRI, VS, or SD of ITI ($p > 0.4$ for all, $N = 39$). The Cz MMN was significantly correlated with the TRI ($\rho = -0.6$, $p = 8.4636e-05$, $N = 40$) and SD of ITI ($\rho = 0.34$, $p = 0.03$, $N = 40$) but not with VS ($\rho = -0.1043$, $p = 0.52$, $N = 40$). Since SD of ITI is more significantly correlated with the TRI, the TRI likely reflects other components in addition to the MMN. For instance, the contribution of the P2 highlighted earlier in supplementals ("Relationship between N1/P2 Difference & Tapping") indicates that the P2 is also a notable contributor to the TRI.

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Chapter 4 BREATHING PRACTICES FOR STRESS AND ANXIETY REDUCTION: CONCEPTUAL FRAMEWORK OF IMPLEMENTATION GUIDELINES BASED ON A SYSTEMATIC REVIEW OF THE PUBLISHED LITERATURE

Abstract

Anxiety and stress plague populations worldwide. Voluntary regulated breathing practices offer a tool to address this epidemic. We examined peer-reviewed published literature to understand effective approaches to and implementation of these practices. PubMed and ScienceDirect were searched to identify clinical trials evaluating isolated breathing-based interventions with psychometric stress/anxiety outcomes. Two independent reviewers conducted all screening and data extraction. Of 2904 unique articles, 731 abstracts, and 181 full texts screened, 58 met the inclusion criteria. Fifty-four of the studies' 72 interventions were effective. Components of effective and ineffective interventions were evaluated to develop a conceptual framework of factors associated with stress/anxiety reduction effectiveness. Effective breath practices avoided fast-only breath paces and sessions <5 min, while including human-guided training, multiple sessions, and long-term practice. Population, other breath paces, session duration ≥5 min, and group versus individual or at-home practices were not associated with effectiveness. Analysis of interventions that did not fit this framework revealed that extensive standing, interruptions, involuntary diaphragmatic obstruction, and inadequate training for highly technical practices may render otherwise promising interventions ineffective. Following this evidence-based framework can help maximize the stress/anxiety reduction benefits of breathing practices. Future research is warranted to further refine this easily accessible intervention for stress/anxiety relief.

Keywords: breathing; breathwork; pranayama; respiration; diaphragmatic; stress; anxiety

Introduction

The rising prevalence of anxiety and chronic stress plagues populations worldwide. Prior to the COVID-19 pandemic, anxiety disorders had already attained startlingly high proportions, affecting nearly one-third of Americans at some point during their lifetime (Kessler et al. 2005). Since then, anxiety disorders have surged by an estimated 25.6% globally (Santomauro et al. 2021) and they burden the economy with healthcare costs and reduced productivity (DuPont et al. 1996; Kalia 2002). Both above and below the clinical threshold, anxiety and chronic stress impact physical, mental, and cognitive health, increasing the risk of cardiometabolic disorders, cancer, mental illness, neurodegenerative disease, and all-cause mortality (Jonas et al. 1997; Rozanski et al. 1999; Reiche et al. 2004; Eaker et al. 2005; Schneiderman et al. 2005; McEwen 2008; Machado et al. 2014; Vyas et al. 2016; Kang et al. 2017; Yaribeygi et al. 2017; Niles and O'Donovan 2019). Chronic activation of the stress response induces allostatic overload, a cumulative "wear and tear" on the brain and body that erodes resiliency and health (McEwen 2008).

Common stress and anxiety treatments rely on external factors, such as a therapist or medication, and come with modest effect sizes (Carpenter et al. 2018) or unfavorable side effects (Bandelow et al. 2017). Effective, accessible, and risk-free solutions are needed.

Voluntary regulated breathing practices may offer such a solution. These practices draw on both modern scientific studies and ancient yogic-pranayama concepts, with applications ranging from clinical anxiety treatment in adults to reducing stress reactivity in college athletes (Han et al. 1996; Sengupta 2012; Sellakumar 2015; Cramer et al. 2018; Hunt et al. 2018). Common voluntary regulated breathing practices include diaphragmatic breathing, paced slow breathing, breathing with biofeedback, and alternate-nostril breathing (ANB). Breathing practices, when used in isolation, have the advantage of being universally accessible, scalable, and cost-free. They are not limited by access to healthcare services nor burdened by side effects and put potential treatment tools in the hands of the individual (Leyro et al. 2021; Malviya et al. 2022; Banushi et al. 2023).

Breathing practices' effects on the autonomic nervous system and brain may underlie their stress-reducing benefits. Effective breathing interventions support greater parasympathetic tone, which can counterbalance the high sympathetic activity intrinsic to stress and anxiety. Respiratory entrainment of brain rhythms offers an additional avenue through which breathing may influence neural circuit dynamics, cognition, and mood (Tort et al. 2018; Ashhad et al. 2022). Breathing also uniquely engages in a reciprocal relationship with stress and anxiety, whereby stress and anxiety can both affect (Bechbache et al. 1979; Grossman 1983; Masaoka and Homma 1997; Martinez et al. 2001; Wilhelm et al. 2001; Nardi et al. 2009) and be affected by (Han et al. 1996; Bhimani et al. 2011; Sellakumar 2015; Hunt et al. 2018) altered respiratory patterns. Due to the shared neurophysiological underpinnings of stress and anxiety, from hereon, the term "stress" is used to encompass both conditions.

Although existing literature confirms the widespread benefits of slow breathing practices for stress/anxiety reduction (Hopper et al. 2019; Leyro et al. 2021; Rung et al. 2021; Malviya et al. 2022; Banushi et al. 2023; Fincham et al. 2023; Miri et al. 2023), null or negative results are reported in some studies (Holmes et al. 1978; Sakakibara and Hayano 1996; Biggs et al. 2003; Jefferson 2010; Lin et al. 2014; Boaviagem et al. 2017; Kamath et al. 2017; Thomas et al. 2017; Ratcliff et al. 2019; Telles et al. 2019; Meier et al. 2021; Aktaş and İlgin 2023). Discerning the distinguishing features between effective and ineffective interventions is of interest.

We conducted a systematic review of clinical studies that evaluated the effectiveness of voluntary regulated breathing practices on psychometric measures of anxiety and stress. We identified intervention characteristics associated with effectiveness and used these data to build a conceptual framework of components associated with the stress reduction effectiveness of breathing practices.

Materials and Methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines were strictly followed throughout. A protocol was not developed or registered.

Overview

We searched peer-reviewed, published literature for original clinical trials evaluating the effectiveness of voluntary regulated breathing practices on psychometric stress and anxiety measures. Our search covered articles published through March 2023, written in English, and from any geographic location. We operationally defined “voluntary regulated breathing practice” as any voluntary, regulated manipulation or control of the breath. We chose a broad and inclusive definition in an effort to capture a variety of regulated breathing methods, including deep breathing, diaphragmatic breathing, yoga or pranayama breathing, slow breathing, paced or patterned breathing, ANB, and more.

Search Strategy

Our search strategy incorporated PubMed and ScienceDirect electronic searches (see Appendix) and manual reference-mining of previously published reviews and key clinical trials (Grossman 1983; Han et al. 1996; Sovik 2000; Pal and Velkumary 2004; Chen et al. 2012; Paulus 2013; Victoria and Caldwell 2013; Jerath et al. 2015, 2019; Ruth 2015; Ma et al. 2017; Zaccaro et al. 2018; Hopper et al. 2019; Saoji et al. 2019; Leyro et al. 2021; Rung et al. 2021; Malviya et al. 2022; Banushi et al. 2023; Fincham et al. 2023; Miri et al. 2023).

Selection Criteria

Publication and Study Type

We included peer-reviewed, published randomized controlled trials (RCT) and other non-randomized prospective cohort and clinical studies. Gray literature, case studies, retrospective observational data analyses, editorials, and reviews were excluded.

Intervention

We included studies that considered any voluntary, regulated breathing practice as its own intervention, whether part of the treatment or control. We excluded interventions that used breath practices in combination with other interventions, such as yoga, meditation, tai chi, etc. We included interventions that used metronomes or visual/audio cues for guiding breathing pace and excluded those in which a device provided real-time biofeedback, such as data on expelled carbon dioxide (CO2), respiratory rate, heart rate variability (HRV), etc. We excluded interventions that incorporated means outside of participants' direct control to manipulate or regulate participants' oxygen or CO2 intake.

Outcomes

We included studies where primary or secondary outcomes incorporated psychometric stress or anxiety measures, defined as those that quantitatively measure stress or anxiety by use of inventory, questionnaire, observation, or self-report. Studies that evaluated fear outcomes or physiologic measures were included only if psychometric measures of stress/anxiety were also included.

Populations

The review included participants with clinical stress or anxiety (e.g., anxiety disorders, post-traumatic stress disorder) and non-clinical stress (e.g., healthy adults, youth, disease-specific populations). Studies with participants aged ≥1 year (i.e., capable of intentional breath regulation), of both genders and of any education or socioeconomic status were included.

Article Screening and Data Extraction

Articles were reviewed in the following stages: 1. Title-screening; 2. Abstract-screening of accepted titles; 3. Full-text screening of accepted abstracts; 4. Data extraction from accepted articles. Two reviewers conducted all levels of screening and data extraction. Discrepancies were resolved through discussion or review by a third reviewer. Data extracted from accepted articles included journal and publication information, participant demographics, inclusion and exclusion criteria, control and intervention descriptions, study duration, outcome measures, results, limitations, and implications (see Appendix). Data collected for framework development comprised details about study design, breath practice, intervention duration, and implementation components, such as use of human-guided training, number of sessions, and use of long-term practice. We defined human-guided training as the use of live or pre-recorded audio or video human guidance during at least the first breath session. Multiple sessions were defined as performing the breathing practice more than once, whether separated by minutes or multiple days. Long-term practice was defined as ≥6 sessions over ≥1 week. Authors were contacted when data were unavailable or unclear.

Assessment of Study Quality

Studies were assessed by two independent reviewers for methodological and reporting quality. Disagreements between reviewers were resolved through discussion or by a third reviewer. RCTs were assessed using a modified form of the Boutron checklist to evaluate a report of a nonpharmacological trial (CLEAR-NPT; see Appendix; Boutron et al. 2005; Chen et al. 2012). Non-RCTs were assessed using the National Heart, Lung, and Blood Institute of the National

Institutes of Health (NHLBI-NIH) quality assessment tool for single-arm, pre-post, or non-randomized studies (see Appendix; NHLBI 2023). For both tools, scores <0.6 were considered poor quality, 0.6–0.8 fair, and >0.80 good. All selected studies were included in data extraction and synthesis, regardless of their methodological quality, as assessed with these tools.

Synthesis

Results were synthesized by first classifying the studies by study population, type, and use of stress/anxiety as a primary versus secondary outcome. Patterns among effective and ineffective interventions were identified based on study design and population and breath practice type, training, duration, and implementation. We compared the frequencies of these data to identify factors associated with intervention effectiveness. Parameters were categorized in n × 2 contingency tables where rows represented parameters and columns represented effectiveness. Fisher's exact tests of independence (Mehta and Patel 1983; Fisher 1992) were performed for each parameter that could be summarized in a contingency table with fixed margins. Interventions for which effectiveness outcomes differed from the above patterns were labeled outlier interventions, details of which were explored through qualitative analysis to provide further insights into effectiveness patterns. Synthesis results were used to create a conceptual framework of intervention characteristics associated with stress reduction effectiveness. Analyses were performed using R Statistical Software (v4.1.2; R Core Team 2021). Results were presented in narrative, tabular, and figure form.

Results

Study Selection and Characteristics

Results of the search and screening process are presented in the PRISMA flow diagram (Figure 4.1). Table 4.1 provides details of all included studies by population and by use of stress/anxiety as the primary or secondary outcome. Six broad population categories emerged: youth (4 studies); healthy adults (14 studies); high-anxiety adults (4 studies); clinical populations (29 studies), divided into chronic-care clinical populations (9 studies), such as those with ongoing asthma or hypertension, and acute-care clinical populations (20 studies), such as those undergoing chemotherapy, dental care, or surgery; and individuals placed in simulated-stress situations (7 studies), such as an artificial public speaking task or electric shock anticipation. Forty-one of the 58 studies were RCTs, and 17 were non-randomized prospective clinical studies. Of the 41 RCTs, 23 included psychometric measures of stress or anxiety as primary outcomes, and 18 included these measures as secondary outcomes. Of the seventeen non-RCTs, 8 included psychometric measures of stress or anxiety as primary outcomes, and 9 did as secondary outcomes. Forty-four of the 58 studies were comparative; comparators were usual care or no intervention in 22 studies, other breath-related interventions in 8 studies, and non-breath-related interventions in 14 studies.

Twenty-five of the 58 studies were conducted in Asia; 14 in Europe; 13 in the United States; 1 in Canada; 2 in Brazil; 2 in North Africa; and 1 in New Zealand. Twenty-nine studies were based in hospital or clinical care settings, such as primary care, medical centers, or other clinical settings. Fifteen were at university settings, including medical schools. Three were based at yoga centers, 2 at elementary or secondary schools, 1 in an automotive assembly plant, and 1 was remote. The remaining 6 settings were unclear.

Within the 58 studies, 72 breathing interventions that met our inclusion criteria were identified, and 54 such interventions significantly reduced participants' stress/anxiety. The most common type of breathing intervention was general slow breathing, which was included in 36 of the studies. The second most common selection was deep diaphragmatic breathing (20), followed by fast breathing (14), alternate or unilateral nostril breathing (ANB, UNB; 11), breathing with holds/pauses (7), extended exhale breathing (6), normal-rate breathing (2), and paced or pursed lip breathing (5).

The following psychometric measures of stress and anxiety were used (Figure 4.2): State Trait Anxiety Inventory (STAI) in 25 studies; Visual Analog Scales (VAS) in 7; Beck Anxiety Inventory (BAI) in 6; Hospital Anxiety and Depression Scale (HADS) in 5; stress/anxiety Likert scales in 5; Perceived Stress Scale (PSS) in 4; Profile of Mood States (POMS) in 2; Burn-Specific Pain Anxiety Scale (BSPAS); Depression Anxiety Stress Scales (DASS) in 1; and other stress/anxiety metrics in 11. Additional metrics were included in some studies to evaluate the impact of breathing interventions on cognition, lung function, physiological stress, psychological well-being, and other health-related conditions.

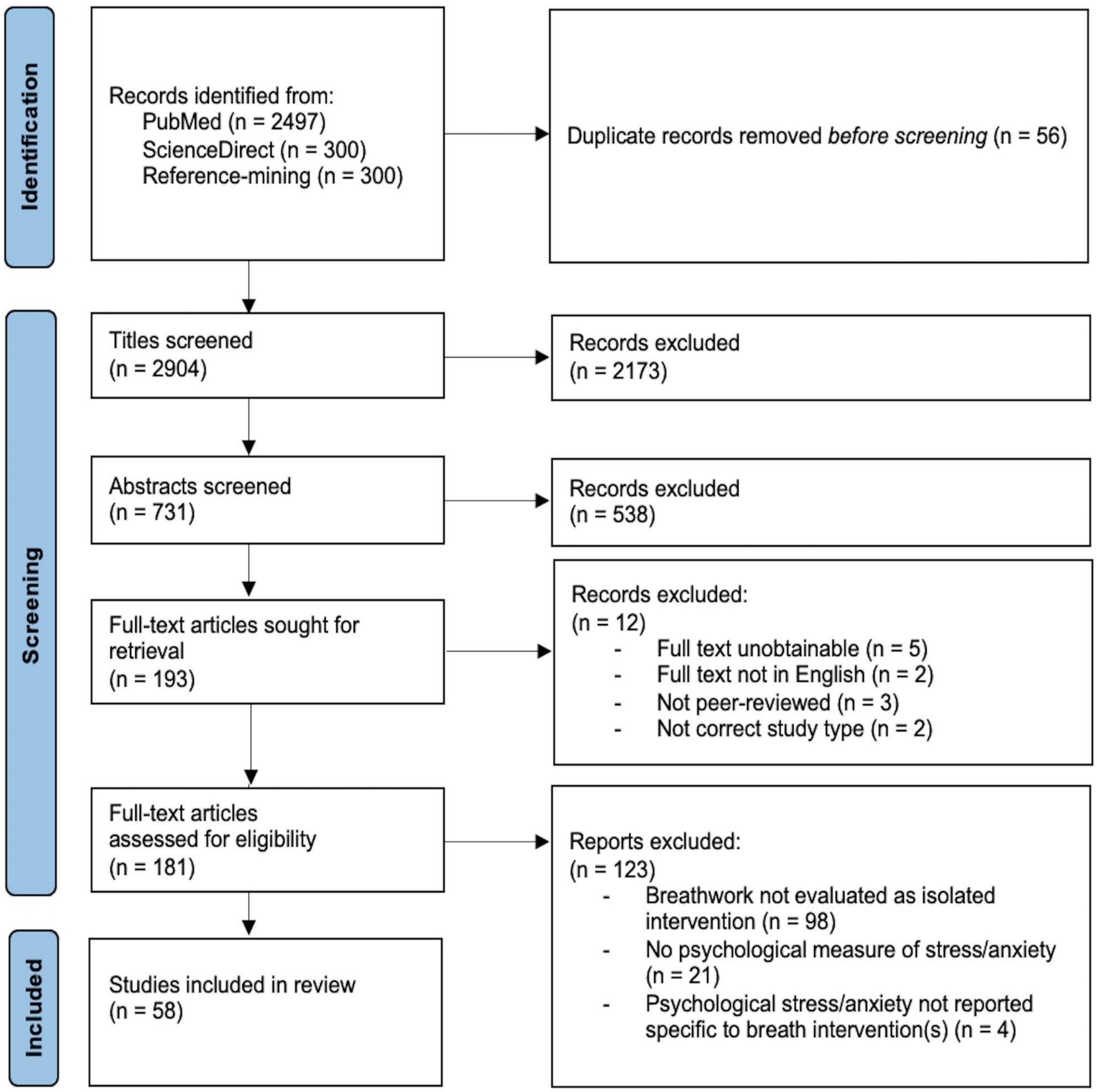

Figure 4.1: Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram of study identification, screening, and selection process. n, number.

Table 4.1: Details of included studies' design and interventions (N = 58) by population and use of stress/anxiety as primary or secondary outcome.

Author, Year, Setting	Study Design, Population	Mean Age (SD), % Female, N	Intervention and Control, Time Frame
			A. Youth
			Youth: Stress/anxiety as primary outcome
*** Sellakumar 2015** India, secondary school (grades 6–12)	RCT Adolescent school students	14 y, 48% Ix: 50 C: 50	Ix: 1-time guided group training followed by 45 days of 30 min individual: **rhythmic breathing, pranayama, SK, slow breathing, deep breathing, prolonged exhales, brief breath-holds** C: No intervention
*** Khng 2017** Singapore, 4 elementary schools	RCT 5th-grade students	Ix: 10.7 y, 48%, 61 C: 10.7 y, 48%, 61	For 10 min prior to and during six 1 min breaks in 2nd administration of math test: Ix: **Deep abdominal breathing**; C: Resting quietly
*** Bargale et al. 2021** India, hospital pediatric dentistry dept.	RCT Children needing dental treatment under anesthesia	51% Ix: 8.5 y (1.9), 30 C: 8.4 y (1.9), 30	Two sessions, before and after anesthetic procedure, of guided: Ix: Slow inhale, 2 s hold, exhale into pinwheel C: **Relaxation breathing,** feeling chest and belly move
			Youth: Stress/anxiety as secondary outcome
*** Hakked et al. 2017** India, swim academy	RCT Competitive youth swimmers	52% Ix: 15.2 y, 14 C: 15.1 y, 13	For 4 wks, regular swim training alongside: Ix: 10 m, 5×/wk in group w/audio-guided yogic breathing practices: * **Sectional (abdominal, thoracic, upper lobar) breathing** * Yogic **bellows breathing** (forceful nasal breathing w/o strain and w/abdominal expansion/contraction) * **ANB w/breath retention** after inhaling C: No intervention
			B. Healthy Adults
			Healthy Adults: Stress/anxiety as primary outcome
*** Gupta et al. 2010** India, yoga training camp	Pre-post trial Married men	60–70 y (range), 0%, 30	7-day group training + 3 mo individual practice of **ANB**
*** Bhimani et al. 2011** India, medical college	Pre-post trial Newly admitted medical students	17–22 y (range), 54%, 59	8 wks of 1 h/day, 5 days/wk instructor-led group **pranayama**: Kapalabhati, External Kumbhaka (Bahya), Easy Comfortable Pranayama (Sukha Purvaka), Surya Bhedan, Ujjayi, Sitkari, Sitali
*** Sharma et al. 2013** India, yoga research center and school	RCT Healthy healthcare students	Ix-1: 18.4 y, 77%, 30 Ix-2: 19.2 y, 87%, 30 C: 18.9 y, 83%, 30	For 12 wks, 30 m/day, 3×/week, of guided group: Ix-1: **Fast pranayama**—repeated cycles of 1 min each kapalabhati, Bhastrika, kukkriya, then 1 min rest Ix-2: **Slow pranayama**—repeated cycles of 2 min each of ANB, 6-3-6-3 breath, extended exhales w/sounds, then 1 min rest * Ix-1 and Ix-2 both end w/10 min shavasana C: No intervention

Table 4.1: Details of included studies' design and interventions (N = 58) by population and use of stress/anxiety as primary or secondary outcome, Continued

Author, Year, Setting	Study Design, Population	Mean Age (SD), % Female, N	Intervention and Control, Time Frame
* **Sundram et al. 2014** Malaysia, automotive assembly plant	Pre/post-test nonequivalent-groups design Male automotive assembly line workers	20+ y (range) Ix: 20+ y, 0%, 468 C: 20+ y, 0%, 293	Ix: Five 10 min group sessions of guided **deep breathing** over 9 mo, +2×/day at-home practice encouraged C: Pamphlet on stress and its ill-effects, w/no stress reduction technique info
* **Schmalzl et al. 2018** US, university town	RCT Yoga-naive healthy adults	Ix: 25 y, 54%, 22 C: 24 y, 61%, 18	8-wk, 2×/wk instructor-led group classes + remaining days 15–20 min video-guided group practice: Ix: Yoga + breathing, equal-paced inhales/exhales, movements paced to breathing, 5 breaths in each pose C: Seated **breath practice**, visualizing breath moving up and down spine, directing breath to specific body parts, short breath holds after inhale/exhale, and ANB
* **Okado et al. 2020** US, university setting	RCT Undergraduate students	19.81 y (2.42) Ix-1: 20.16 y (3.80), 45.5%, 20 Ix-2: 19.40 y (1.75), 72.1%, 31 Ix-3: 19.68 y (1.74), 68.2%, 30 C: 19.99 y (2.37), 79%, 64	1 in-person session followed by 2 wks of individual practice: Ix-1: Guided **diaphragmatic breathing** Ix-2: Relaxation techniques, asked to identify relaxation strategies in session Ix-3: Identical to Ix-2, +activity handout w/behavioral strategies to promote relaxation C: No intervention
* **Magnon et al. 2021** France, setting unclear	Single-arm study Healthy older and young adults	41.2 y (23.6), 80.9%, 47 Older: 65.9 y (5.1) Young: 19.6 y (1.6)	Single 5 min session of **slow breathing** following on-screen moving drop of water; starting w/4 s inhale/exhale, gradually extending exhale to 6 s
* **Balban et al. 2023** US, remote setting	RCT Adults w/o severe psychiatric or medical conditions	27.97 y, 68.5% Ix: 84 C: 24	28 days of daily 5 min home practice: Ix-1: **Cyclic sighing**: inhale slowly, inhale once more, slowly exhale all breath Ix-2: **Box breathing**: individualized pace w/equal length inhale, exhale, and breath holds Ix-3: **Cyclic hyperventilation w/retention**: 3 rounds of 30 deep inhales w/passive exhale, ending w/15 s hold C: Mindfulness meditation: sit/lie down, close eyes, breathe, focus on forehead between eyes
Healthy Adults: Stress/anxiety as secondary outcome			
* **Busch et al. 2012** Germany, university setting	Pre-post trial of 2 Ix's separated by 6 mo Healthy undergraduate students	25 y, 87%, 15	6 weekly sessions of 20 min instructor-guided DSB, 7 bpm: Ix-1: **DSB** alone; Ix-2: DSB w/attentive concentration respiratory feedback task

Table 4.1: Details of included studies' design and interventions (N = 58) by population and use of stress/anxiety as primary or secondary outcome, Continued

Author, Year, Setting	**Study Design, Population**	**Mean Age (SD), % Female, N**	**Intervention and Control, Time Frame**
Lin et al. 2014 Taiwan, university setting	Within-subjects, 4-arm trial Healthy college students	20.98 y (1.03), 78.7%, 47	5 min sitting then **paced breathing** using on-screen pacer for 2 min per pattern w/1 min rest between Ix-1: **6 bpm, 5-0-5-0**; Ix-2: **6 bpm, 4-0-6-0**; Ix-3: **5.5 bpm, 4.4-0-6.6-0**; Ix-4: **5.5 bpm, 5.5-0-5.5-0**
* **Hunt et al. 2018** US, large private university	RCT Collegiate varsity soccer, swimming, track athletes	20 y, 59%, 76	10 min metronome-guided **paced breathing at 6 bpm** followed by either: Ix: **5 min guided + 5 min unguided DB**, aiming for 4 bpm C: 10 min guided PMR Afterwards, all did 5 min paced breathing (6 bpm) followed by cognitive stressor challenge
* **Naik et al. 2018** India, medical school	RCT Healthy adult male volunteers	Ix: 24.45 y, 0%, 49 C: 24.12 y, 0%, 50	For 12 wks: Ix: 5×/wk of 30 min guided **modified ANB** (6-6-6-0) + instructions to practice at home other 2 days/wk C: No Ix
* **Conlon et al. 2022** UK, University of Bath	RCT Collegiate and National Team level athletes w/no formal shooting experience	20.17 y (2.77) Ix-1: 60.9%, 23 Ix-2: 60.9%, 23 C: 57.1%, 21	Between 2 shooting task exercises, 5 min guided training + 5 min pacer-guided practice w/nasal inhales, pursed-lip exhales of: Ix-1: 4 s inhale, 6 s exhale (6 bpm) **diaphragmatic breathing** Ix-2: **2.5 s inhale, 2.5 s exhale** (12 bpm) paced breathing C: Watched 10 min respiratory anatomy educational video
* **Schlatter et al. 2022** France, university medical school	RCT 5th-yr anesthesiology and critical care residents participating in simulations for medical training	29 y (1) Ix-1: 50%, 12 Ix-2: 27%, 11 C: 46%, 11	For 5 min before engaging in 15 min simulated medical scenario w/performance evaluation: Ix-1: **Relaxing breathing** w/4 s inhale, 6 s exhale, following moving cursor on computer Ix-2: Same as Ix-1, but w/HRV biofeedback and instructions to increase HRV C: Read lab test results
C. High-Anxiety Populations			
High-Anxiety Populations: Stress/anxiety primary outcome			
* **Clark and Hirschman 1990** US, inpatient alcohol rehabilitation facility	RCT Male, alcohol-dependent inpatients scoring high trait anxiety (STAI > 46.62)	39.3 y Ix: 0%, 18 C: 0%, 18	Two 10 min sessions, 2 days apart, w/audio pacing tones in 1st session and no sound in 2nd: Ix: **Guided slow breathing** (10 bpm) at audio tone pace session 1; at same yet self-guided pace session 2 C: Count audio tones session 1, relax session 2
* **Chen et al. 2017** Taiwan, medical center	RCT High-anxiety adults from outpatient psych unit	Ix: 24 y (6), 60%, 15 C: 25 y (7), 73%, 15	12 individual training sessions over 8 wks + 2×/day home practice of: Ix: **Guided diaphragmatic breathing** C: "Routine respiration"

Table 4.1: Details of included studies' design and interventions (N = 58) by population and use of stress/anxiety as primary or secondary outcome, Continued

Author, Year, Setting	Study Design, Population	Mean Age (SD), % Female, N	Intervention and Control, Time Frame
* **Serafim et al. 2019** Brazil, hospital	Pre-post open-label uncontrolled clinical trial Outpatients w/stable BD and complaints of anxiety	42.8 y, 70%, 14	Ix: 4 weekly 1:1 **guided deep breathing** trainings of 7, 10, 15, and 20 m, respectively, followed by at-home practice for 1 wk
High-Anxiety Populations: Stress/anxiety as secondary outcome			
* **Clark et al. 1985** UK, setting unclear	AB case series Outpatient adults with frequent panic attacks and associated anxiety	36 y, 72%, 18	Ix: 2 sessions, w/1 wk between, of 2 min voluntary hyperventilation+ discussion of over-breathing and panic attacks, followed by **guided slow breathing** Before and after Ix, 11 were exposed to individually determined anxiety-provoking situation
D. Clinical Populations (Acute)			
Clinical Populations (Acute): Stress/anxiety as primary outcome			
Biggs et al. 2003 US, private dental practice	RCT Patients seeking dental treatment	38 y, 58%, 272	Written instruction in waiting room: Ix-1: **Unguided deep diaphragmatic breathing** Ix-2: Focused attention on non-teeth body part C: No intervention
* **Hayama and Inoue 2012** Japan, hospital inpatient	RCT Women w/recent Dx of gynecological cancer undergoing 1st chemo Tx	Ix: 53.6 y (9.4), 100%, 11 C: 61.7 y (9.8), 100%, 12	Ix: Before 1st chemo session and on days 2, 4, 6 post-chemo, 10 min of 4-step individual **guided diaphragmatic breathing** of 10 deep inhales and slow exhales per step, done lying down: breaths 0–10 and 30–40 w/arms raised; 11–20 abdominal and 21–30 thoracic breathing C: Usual chemo + nursing care
* **Valenza et al. 2014** Spain, hospital	RCT COPD exacerbation patients	Ix: 76 y, 0%, 23 C: 74.4 y, 0%, 23	Ix: 10-day, 2×/day 30 m, guided breathing of **inspiratory muscle relaxation, pursed lip breathing, prolonged and active expiration** C: Standard care
* **Bidgoli et al. 2016** Iran, hospital	RCT Patients undergoing first coronary angiography and experiencing anxiety	Ix: 55.5 y, 55%, 40 C: 62.7 y, 45%, 40	Ix: Single session before surgery of 5 min guided **sukha pranayama**—slow, rhythmic breathing w/equal length inhales-exhales C: Routine care
Boaviagem et al. 2017 Brazil, maternity hospital	RCT Nulliparous women in active labor, 37–41 wks gestation	Ix: 21.2 y, 100%, 60 C: 20.6 y, 100%, 61	Ix: Instruction to use **slow deep breathing** (5 s inhales, 5 s pursed lip exhales) during dilation, active, late labor phases, including post-exhale pause (1–2 s) for active and late active labor only C: Standard care

Table 4.1: Details of included studies' design and interventions (N = 58) by population and use of stress/anxiety as primary or secondary outcome, Continued

Author, Year, Setting	Study Design, Population	Mean Age (SD), % Female, N	Intervention and Control, Time Frame
*** Cicek and Basar 2017** Turkey, hospital delivery room	RCT Nulliparous women 38–42 wks pregnant w/o complications in early labor	Ix: 23.3 y, 100%, 35 C: 22.4 y, 100%, 35	Ix: 30 min **guided Lamaze breath** stages for progressive labor w/real-time guidance during labor of normal nasal, slow deep chest, rapid shallow, rapid abdominal C: Routine hospital checks only
*** Chandrababu et al. 2019** India, hospital	Non-randomized 2-arm trial Patients undergoing 1st-time cardiac surgery	58.7 y Ix: 25%, 24 C: 29%, 24	Ix: 15 min **guided ANB**, taught 2 days prior to surgery and performed on days 3–5 post-surgery C: Usual pre- and post-operative care
Ratcliff et al. 2019 US, university medical center	RCT Women scheduled for stereotactic breast biopsy	55.4 y (11.27) Ix-1: 55.1 y, 100%, 30 Ix-2: 55.1 y, 100%, 30 C: 55.9 y, 100%, 16	10 min prior to and throughout biopsy, guided: Ix-1: Mindfulness meditation; Ix-2: **Diaphragmatic breathing** C: Listened to neutral-content audio
*** Grinberg et al. 2020** US, medical center	Non-randomized pre-post study Male veterans scheduled for prostate biopsy	66.9 y (6.46) Ix: 66.7 y, 0%, 20 C: 65.05 y, 0%, 20	Ix: 15 min **guided diaphragmatic breathing** immediately prior to biopsy C: Standard care
*** Abo El Ata et al. 2021** Egypt, hospital	Pre-post study Burn patients during dressing changes	28.8 y (8.9), 37%, 7	2 wk daily **guided relaxation breathing** exercises before and during daily dressing change
*** Hosseinzadeh-Karimkoshteh et al. 2021** Iran, medical center	RCT Burn patients	Ix: 25.5 y, 33.3%, 15 C: 28.1 y, 40%, 15	4 days of: Ix: 30 min **guided relaxation breathing** before dressing change, 4-4-4-0 pursed-lip exhales C: Routine care
*** Zahn and Kuonen 2021** Switzerland, university hospital	RCT Adults having dermatological surgery w/local anesthesia	Ix: 60.7 y (20.6), 40.8%, 86 C: 60.2 y (18.9), 48.8%, 84	Before undergoing surgery: Ix: **Deep breathing instruction**, were told to perform before and during procedure C: No Instruction
*** Moghadam et al. 2022** Iran, psychiatric hospital	RCT Adults receiving ECT for depression	Ix-1: 35 y (14), 50%, 30 Ix-2: 38 y (9), 53.3%, 30 C: 36 y (10), 50%, 32	Before ECT procedure: Ix-1: 10 min **guided slow breathing**, (5 s deep nasal inhale, 5 s mouth exhale) Ix-2: 3–5 min breathing lavender aromatherapy oil C: Routine care

Table 4.1: Details of included studies' design and interventions (N = 58) by population and use of stress/anxiety as primary or secondary outcome, Continued

Author, Year, Setting	Study Design, Population	Mean Age (SD), % Female, N	Intervention and Control, Time Frame
* **Aktas and Ilgin 2023** Turkey, Ankara Hospital	RCT Postoperative bariatric surgery patients	34.7 y Ix-1: 76.7%, 23 Ix-2: 66.7%, 20 C: 53.3%, 16	Each h during post-op h's 1-6: Ix-1: **4-7-8 breathing technique**, 10 breaths; Ix-2: **Deep breathing**, 4 breaths C: Treatment as usual
Clinical Populations (Acute): Stress/anxiety as secondary outcome			
* **Dhruva et al. 2012** US, university medical center	RCT w/single-arm crossover Cancer patients undergoing intravenous chemo	Ix: 52 y, 75%, 8 C: 56 y, 100%, 8	During 2 consecutive chemo cycles: Ix: Usual care + 60 min class 1×/wk + 2×/day of 10–15 min **individual home pranayama**: * breath observation * ujjayi breathing: slow, deep abdominal rhythmic inhales/exhales, w/extended exhales and partially closed glottis * kapalabhati breathing: gentle inhales, brief pause, forceful exhale * ANB C: Usual care for 1st chemo cycle; usual care + Ix for 2nd cycle
* **Park et al. 2013** South Korea, medical center	Pre-post study comparison group Burn patients	44.9 y Ix: 44.5 y, 43.3%, 30 C: 45.3 y, 60%, 30	Over 3 days: Ix: **Guided relaxation breathing** 4-0-4-0 before and 4-0-2-0 during dressing changes C: Usual dressing change procedure
* **Eldin et al. 2015** Libya, hospital	RCT Burn patients	Ix: 18–50 y, 45%, 20 C: 18–50 y, 30%, 20	Over 3 days: Ix: 15+ min **guided relaxation breathing** (in-nose, out-mouth) C: Standard care
* **Iyer et al. 2020** India, medical center	Pre-post Burn patients	31.8 y (17.8), 35%, 20	Over 7 days: Ix: 15 m/day **guided deep breathing**
* **Ursavas and Catakli 2020** Turkey, hospital	RCT Total knee replacement patients	Ix: 65 y, 79%, 19 C: 69 y, 79%, 19	Ix: **Guided diaphragmatic breathing** + instruction to use at 1, 2, 4, 8, 12, and 24h post-op + when experiencing pain/anxiety C: Standard care
* **Lu et al. 2022** China, hospital	RCT Lung cancer patients undergoing thoracic surgery	59.3 y (10.2) Ix: 55%, 34 C: 61%, 34	Over 14 days: Ix: 2×/day of 15–20 min **guided Active Cycle of Breathing Technique**, each part repeated 3–5×: slow inhale, 3 s hold, 6 s pursed-lip exhale; deep active inhale, 3 s hold, passive exhale (all nasal; slow deep nasal inhale, 2–3 forceful "huff" mouth exhales) C: Usual care

Table 4.1: Details of included studies' design and interventions (N = 58) by population and use of stress/anxiety as primary or secondary outcome, Continued

Author, Year, Setting	Study Design, Population	Mean Age (SD), % Female, N	Intervention and Control, Time Frame
		E. Clinical Populations (Chronic)	
		Clinical Populations (Chronic): Stress/anxiety as primary outcome	
* **Marshall et al. 2014** US, setting unclear	Pre-post repeated-measures trial Post-stroke individuals w/brain damage, w and w/o aphasia	55.6 y, 18%, 11	4 wks of 1 h guided practice 1×/wk, followed by 6 wks of 5–40 min independent practice of **right UNB**: occlude left nostril while inhaling and exhaling through the other, work toward exhaling twice as long as inhale
		Clinical Populations (Chronic): Stress/anxiety as secondary outcome	
* **Han et al. 1996** Belgium, setting unclear	Pre-post single-arm trial Adults w/HVS	37 y, 65%, 92	17 sessions over 2.5 mo of physiotherapist-guided breathing therapy and retraining: * 1st session: 3 min **voluntary hyperventilation** at 60 bpm followed by therapy to reattribute cause of daily life complaints to hyperventilation and explain breath retraining purpose * Remaining sessions: 45 min breath retraining w/**abdominal breathing and slowed exhales**
* **Thomas et al. 2009** UK, primary care general practices	RCT Adults w/asthma and impaired health status	Ix: 46 y (median), 58%, 66 C: 46 y (median), 64%, 63	Ix: 3 physiotherapist-guided sessions w/2–4 wks between each: * One 1 h small group breathing education session * Two 30–45 min individual **DB and nasal breathing** training sessions * Participants instructed to practice breathing exercises ≥10 m/day C: Asthma nurse-delivered education
Jefferson 2010 US, setting unclear	RCT African-American females w/hypertension	Ix: 54 y, 100% C: 56 y, 100%	Ix: 20 min therapeutic chair massage C: Education on **DB**
* **Sureka et al. 2014** India, prison hospital	RCT Adult male prisoners w/psychiatric disorder	Ix: 36 y, 0%, 116 C: 36 y, 0%, 115	For 6 wks, 30 m/day: Ix: Guided **SKY breathing**: 8 min Ujjayi, 5 min bellows (Bhastrika) followed by Om Chant, 10 min SK, and 5 min ANB C: Seated w/eyes closed and gentle attention on breath
* **Sureka et al. 2015** India, prison hospital	RCT Male inmates w/substance dependence	Ix: 39.3 y, 0%, 55 C: 38.8 y, 0%, 56	For 6 wks, 23 m/day: Ix: Guided **SKY breathing**: 8 min Ujjayi, 5 min bellows (Bhastrika), and 10 min SK C: Sitting, eyes closed, attention to breath

Table 4.1: Details of included studies' design and interventions (N = 58) by population and use of stress/anxiety as primary or secondary outcome, Continued

Author, Year, Setting	**Study Design, Population**	**Mean Age (SD), % Female, N**	**Intervention and Control, Time Frame**
Thomas et al. 2017 UK, general practices	RCT Adults w/impaired asthma control	Ix-1: 56 y, 63%, 261 Ix-2: 55 y, 69%, 132 C: 57 y, 63%, 262	Ix: **Guided breath training** delivered either via DVD (Ix-1) or 3 biweekly 30–40 min sessions w/physiotherapist (Ix-2), comprising: nose breathing, abdominal breathing, slow breathing, controlled breath holding, relaxation C: Usual care
*** Fiskin and Sahin 2018** Turkey, medical center	RCT Pregnant women w/GDM	Ix: 30.6 y, 100%, 30 C:31.3 y, 100%, 30	30 days of: Ix: Unguided **diaphragmatic breathing**, 5 min in the morning before leaving bed C: Standard care, invited to talk about their pregnancies 2×/mo
* Watson et al. 2022 New Zealand hospital	RCT (cross-over) Postmenopausal women w/stress cardiomyopathy	66.8 y (2.7) Ix: 100%, 12 C: 100%, 12	One 3 min session each, separated by 5 days, of guided: Ix-1: **Hyperventilation**; Ix-2: **Slow breathing w/3 s hold**
F. Simulated Stress			
Simulated Stress Populations: Stress/anxiety as primary outcome			
Kamath et al. 2017 India, medical school	RCT Healthy, yoga-naive undergrad medical students	Range 19–24 y Ix: 60%, 15 C: 80%, 15	After brief instruction and practice for 15 min prior to **simulated public speaking** task: Ix: Guided **ANB** C: Sitting in quiet room
Simulated Stress Populations: Stress/anxiety as secondary outcome			
Holmes et al. 1978 US, university setting	3-arm clinical trial (randomization/Tx allocation unclear) Undergraduate students	Age not reported, 54%, 111	90 s threat of electric shock (never administered) or visual stimulation, after 5 min of: Ix-1: **Respiration tracing**, breathing at pace where real-time respiration polygraph pen matched previously recorded resting respiration polygraph Ix-2: Attention tracing, using hand-held knob to follow previously recorded resting respiration polygraph recording C: Sitting quietly and relaxing
*** McCaul et al. 1979** US, university setting	RCT, 3 × 2 + 1 factorial-designed Male undergraduate students	Ix-1: 0%, 29 Ix-2: 0%, 28 Ix-3: 0%, 28 C: 0%, 14 (Ages not Reported)	3 groups threatened w/impending electric shock, w/possibly 2 min (duration unclear) of unguided: Ix-1: **Slow-pace regulated breathing** (8 bpm); Ix-2: Normal-pace regulated breathing (16 bpm); Ix-3: Non-regulated breathing C: No breath pacing, no expectations, no threat, anticipation of visual stimulation Ix-1 and Ix-2 had 2 min practice before threat
Sakakibara and Hayano 1996 Japan, university setting	RCT Healthy college students	23 y Ix-1: 40%, 10 Ix-2: 30%, 10 C: 50%, 10	Prior to 2 min threat (electric shock) anticipation w/15 bpm paced breathing, 5 min of unguided: Ix-1: **Slow breathing (8 bpm)** Ix-2: **Fast breathing (30 bpm)** C: Spontaneous breathing

Table 4.1: Details of included studies' design and interventions (N = 58) by population and use of stress/anxiety as primary or secondary outcome, Continued

Author, Year, Setting	**Study Design, Population**	**Mean Age (SD), % Female, N**	**Intervention and Control, Time Frame**
* Telles et al. 2019 India, residential yoga center	Randomized cross-over study Adult males w/yoga breathing experience	28.4 y (8.2), 0%, 50	In 3 separate, 18 min sessions across 3 days, w/timed shape and size discrimination task before/after each: Ix-1: **ANB** Ix-2: Breath awareness C: Quiet sitting
Meier et al. 2021 Canada, setting unclear	RCT Young healthy men and women	23.8 y (4.5), 51%, 35 Ix-1: 12 Ix-2: 11 C: 12	30 m, prior to simulated stress test (modified TSST-G): Ix-1: Guided **relaxation breathing** while standing Ix-2: Laughter yoga C: Reading magazines or books
*** Sharma et al. 2022** India, university setting	Randomized cross-over study University males w/yoga breathing experience	24 y (4), 0%, 38	6 breath sessions in random order, w/timed SLCT before/after each, for 18 min w/1 min rest every 5 m, guided: Ix-1: **ANB**; Ix-2: **Bellows breathing**; Ix-3: **Bumblebee breathing**; Ix-4: **High-frequency breathing** at 50–65 bpm; Ix-5: Breath awareness; Ix-6: Quiet seated rest

Interventions in red font were ineffective for stress outcome (i.e., did not significantly reduce participants' stress/anxiety). Bolded phrases in "Intervention and Control" column reflect key practice details. Bolded author names/years with asterisk (*) represent studies with at least one intervention that did significantly reduce participants' stress/anxiety. ANB, alternate-nostril breathing; betw, between; BD, bipolar disorder; bpm, breaths per minute; chemo, chemotherapy; C, control; chemo, chemotherapy; COPD, chronic obstructive pulmonary disease; dept, department; DSB, deep slow breathing; DB, diaphragmatic breathing; DVD, digital versatile disc; Dx, diagnosis; ECT, electroconvulsive therapy; GDM, gestational diabetes mellitus; h, hour; HR, heart rate; HVS, hyperventilation syndrome; Ix, intervention; min, minutes; mo, month; N, number of subjects; PMR, progressive muscle relaxation; RCT, randomized controlled trial; s, seconds; SD, standard deviation; SK, Sudarshan Kriya; SLCT, Six-Letter Cancellation Test; TSST-G, Trier Social Stress Test for Groups; Tx, treatment; UNB, unilateral nostril breathing; vs., versus; w/, with; w/o, without; wks, weeks; y, years. Practices with numerical annotations such as 4-4-4-0 reflect [inhale count]-[hold count]-[exhale count]-[hold count].Twenty-five of the 58 studies were conducted in Asia; 14 in Europe; 13 in the United States; 1 in Canada; 2 in Brazil; 2 in North Africa; and 1 in New Zealand. Twenty-nine studies were based in hospital or clinical care settings, such as primary care, medical centers, or other clinical settings. Fifteen were at university settings, including medical schools. Three were based at yoga centers, 2 at elementary or secondary schools, 1 in an automotive assembly plant, and 1 was remote. The remaining 6 settings were unclear.

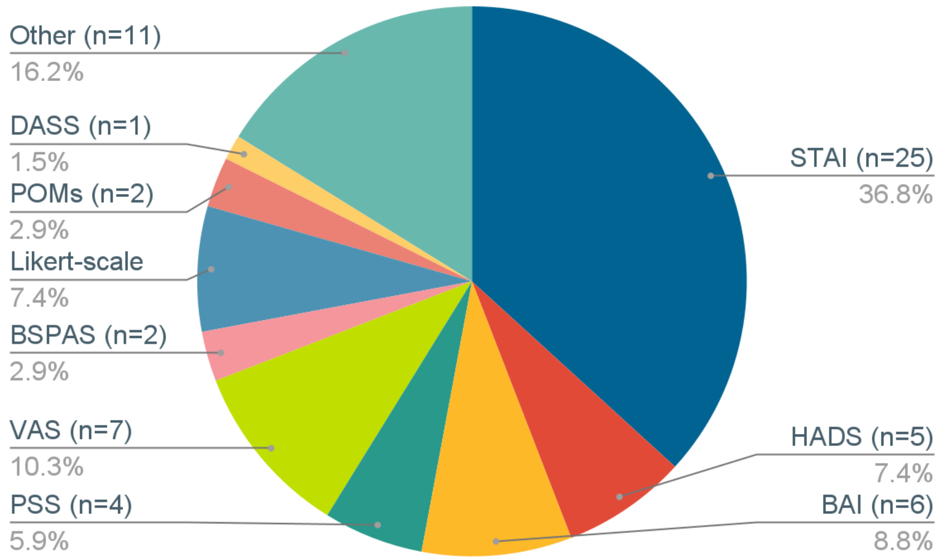

Figure 4.2: Distribution of stress/anxiety outcome metrics used in included studies. Distribution of stress/anxiety outcome metrics used in included studies. Rounding errors result in whole-number percentages summing to more than 100%. Total number of studies using metrics sums to more than 58 because some studies incorporated more than one outcome metric. STAI, State-Trait Anxiety Inventory; HADS, Hospital Anxiety and Depression Scale; BAI, Beck Anxiety Inventory; PSS, Perceived Stress Scale; POMS, Profile of Mood States; BSPAS, Burn-Specific Pain Anxiety Scale; DASS, Depression Anxiety Stress Scale; VAS, Visual Analog Scale

Study Characteristics and Outcomes by Population

Supplemental Table 4.2 describes the stress/anxiety metrics, outcomes, and quality scores of included studies by population.

Youth

Four studies were conducted among youth, of which all were RCTs, and three examined stress or anxiety as a primary outcome. Sample sizes ranged from 27 to 154, mean age from 8 to 15 years, and intervention duration from 1 to 45 days. Of the four interventions in these studies, three used slow breathing and one included a mix of slow breathing, fast breathing, and ANB. All four yielded significant stress/anxiety benefits.

Healthy Adults

Fourteen studies were conducted among healthy adults, of which eight were RCTs and eight examined stress or anxiety as a primary outcome. Sample sizes ranged from 16 to 761, age from 17 to 70 years, and intervention duration from 1 to 273 days. Of the 21 interventions in these studies, 13 used slow breathing, 1 used regular-paced breathing, 1 used cyclic hyperventilation with holds, 1 used fast pranayama, 1 used slow pranayama, 1 used slow and fast pranayama, 2 used ANB, and 1 included a mix of slow breathing and ANB. Seventeen interventions yielded significant stress/anxiety benefits.

High-Anxiety Populations

Four studies were conducted among high-anxiety populations, of which two were RCTs and three examined stress or anxiety as a primary outcome. Sample sizes ranged from 18 to 46, mean age from 24 to 43 years, and intervention duration from 2 to 56 days. All four interventions in these studies incorporated some type of deep, diaphragmatic and/or slow breathing, and all yielded significant stress/anxiety benefits.

Clinical Populations, Acute

Of the 20 studies conducted in clinical settings among populations with acute clinical conditions, 15 were RCTs and 16 examined stress or anxiety as a primary outcome. Sample sizes ranged from 20 to 272, mean age from 21 to 75 years, and intervention duration from 1 to 56 days. Of the 21 interventions in these studies, one used ANB, three included a mix of slow and fast breathing, and the rest used slow breathing. Seventeen interventions yielded significant stress/anxiety benefits.

Clinical Populations, Chronic

Of the nine studies conducted in clinical settings among populations with chronic health conditions, six were RCTs and three examined stress or anxiety as a primary outcome. Sample sizes ranged from 11 to 655, mean age from 31 to 67 years, and intervention duration from 1 to 182 days. Of the eleven interventions used within these studies, six used slow breathing, one used fast breathing, one used UNB, and three included a mix of fast and slow breathing. Seven interventions yielded significant stress/anxiety benefits.

Simulated Stress Settings

Of the seven studies conducted among populations undergoing simulated stress situations, five were RCTs and three examined stress or anxiety as a primary outcome. Sample sizes ranged from 30 to 111, mean age ranged from 23 to 28 years among studies reporting mean data and from 19 to 24 among studies not reporting means, and intervention duration for all was one day. Of the eleven interventions in these studies, six used slow breathing, one used regular-paced breathing, one used fast breathing, one used fast pranayama, and two used ANB. Five interventions yielded significant stress/anxiety benefits.

Study and Reporting Quality

Of the 58 included studies, 7 RCTs and 0 non-RCTs received "good" quality ratings, 20 RCTs and 9 non-RCTs received "fair" ratings, and 14 RCTs and 8 non-RCTs received "poor" ratings (Supplemental Table 4.2). Figure 4.3 summarizes the top identified quality issues. Among RCTs, the main concerns related to the absence of the following: blinding, intention-to-treat analysis, concealed treatment allocation, and analytic consideration of between-group differences in lost-to-follow-up and withdrawals. Among non-RCTs, the main concerns related to the absence of the following: repeated measurements, assessor blinding, population inclusiveness, adequate sample size, and intervention description in the report. The reviewers noted other common quality issues during abstraction. Many pre-post studies did not include a control group, and those that did lacked an active control. Several intervention descriptions were vague and lacked detail about factors such as breath rate, bpm, and instructions for breath practices. Adherence and compliance with at-home practice were measured and reported poorly or not at all, and reports on human-guided training lacked detail in duration, timeline, and extent of guidance.

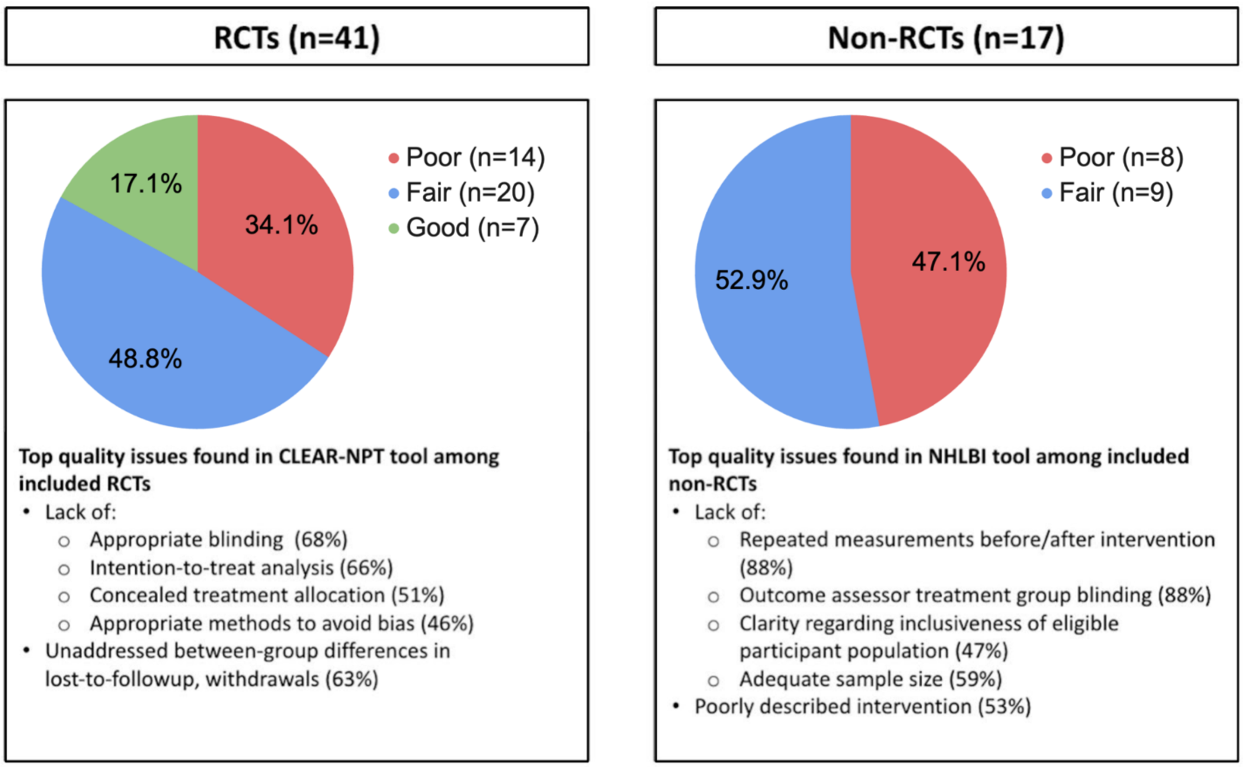

Figure 4.3: Top quality issues in 58 studies included in review by study type. Quality score calculated by dividing number of met criteria by number of applied criteria and normalizing to 0–1.0 range. Quality score categories defined as follows: <0.6, poor; 0.6–0.8, fair; and >0.80, good. CLEAR-NPT, checklist to evaluate a report of a nonpharmacological trial; NHLBI, National Heart, Lung, and Blood Institute; RCT, randomized controlled trial.

Synthesis Results

Study Design Parameters

The following study design parameters were identified for analysis regarding their association with intervention effectiveness: study type (RCT, non-RCT); stress/anxiety as the primary or secondary outcome; control group type (usual care/no intervention, breath practice + other components, such as yoga or meditation, non-breath active control, meditation or mindfulness, no control); and the number of stress/anxiety outcome measurements (1, 2, 3+).

None of the study design parameters were significantly associated with intervention effectiveness (Table 4.2). RCTs made up 72% of effective (39 of 54) and 67% of ineffective (12 of 18) interventions, with these proportions not differing significantly ($p = 0.78$). Stress/anxiety was a primary outcome in 67% of effective and 61% of ineffective interventions ($p = 0.67$). There was no association between effectiveness and use of control group ($p = 0.19$). Stress/anxiety was measured as follows: once in 4% (2 of 54) of effective and 6% (1 of 18) of ineffective interventions; twice, once before and once after the intervention, in 54% and 67% of the respective interventions; and three or more times in 43% and 28%, respectively ($p = 0.43$).

Table 4.2**:** Association of intervention parameters with intervention stress/anxiety reduction effectiveness among 72 included interventions.

Parameter	**N**	***p*-Value**
Study design		
Study design (RCT vs. other)	72	0.77
Control group (yes/no)	72	0.19
Primary vs. Secondary stress/anxiety outcome metric	72	0.78
# stress/anxiety outcome measurements (1, 2, 3+)	72	0.43
Breath practice and implementation		
Population	72	0.14
Breath practice pace	72	0.01 *
Breath pace other than fast-only	70	0.10
Human-guided training (yes/no)	72	<0.001 *
# human-guided sessions (0, 1, 2−3, 4+)	71	<0.001 *
Human-guided training included within device-guided interventions (yes/no)	15	0.03 *
Single vs. Multiple sessions	72	<0.001 *
Long-term vs. No long-term practice	72	0.005 *
Intervention duration (1, 2−5, 6−30, or 31+ days)	71	<0.001 *
Session duration:		
<5, 5–10, 11–20, or >20 m	61	0.03 *
<5 or ≥5 m	61	0.005 *
Among sessions ≥5 m: 5–10, 11–20, or >20 m	52	0.81
Group vs. individual practice vs. both	67	0.79
At-home practice (yes/no)	72	0.24

N reports the number of interventions in which parameter value was reported and thus the number of interventions included in the corresponding Fisher's exact test. *p*-values based on Fisher's exact tests on two-way frequency tables of effective versus ineffective interventions that either did or did not implement each parameter (Supplemental Table 4.1 shows frequency counts; Supplemental File S2 shows statistical tests). *p*-value ≤ 0.05 signifies that intervention effectiveness was not associated with that parameter. Highlighted parameters identified as components for conceptual framework of factors associated with effectiveness in the 72 stress reduction breathing interventions among the 58 studies included in this review. Control categories defined as follows: yes, active and/or non-active control; or no, no control or another breath intervention only. Population categories defined as youth, healthy adults, high-anxiety populations, clinical populations (acute), clinical populations (chronic), and simulated stress populations. Breath practice pace defined as slow only, fast only, combined fast and slow with or without ANB/UNB, and ANB/UNB alone. Human-guided training defined as use of live or pre-recorded audio or video human instruction throughout at least the initial breath session. Multiple sessions defined as performing breathing practice more than once. Long-term practice defined as performing ≥6 sessions over ≥1 week. m, minutes; vs., versus; #, number. * *Statistical significance at $p < 0.05$.*

Breathing Practice and Implementation Parameters

The following breath practice and intervention implementation parameters were identified for analysis: population category; type and pace of breath practice (slow-only, fast-only, a combination of fast and slow with or without ANB/UNB, regular pace, ANB/UNB alone); the use of human-guided training (yes/no); number of human-guided sessions (0, 1, 2–3, 4+); among device-guided interventions, use of human-guided training (yes/no); number of sessions (single or multiple); long-term practice (≥6 sessions over ≥1 week, yes/no); intervention duration (1, 2–5, 6–30, or 31+ days); session duration (<5, 5–10, 11–20, or >20 min); group- or individual-only or group + individual practice; and inclusion of at-home individual practice (yes/no).

Intervention effectiveness was not significantly associated with population category (p = 0.14), session duration beyond 5 min (p = 0.81), group versus individual versus group + individual practice (p = 0.79), and use of at-home practice (p = 0.24; Table 4.3). Among youth and high-anxiety adults, all interventions were effective. Among healthy adults, 17 of 21 (81%) interventions were effective; these numbers were 17 of 21 (81%) among acute clinical populations, 7 of 11 (64%) among chronic clinical populations, and 5 of 11 (45%) among simulated stress populations. The majority of interventions were individual-only (61% of effective and 56% of ineffective interventions) or group-only (28% and 33%, respectively), with 6% of effective and 0% of ineffective interventions including both group and individual sessions. Five interventions were unclear about this parameter in the published paper. Session durations ranged from 1.3 to 60 min for effective and 1–45 min for ineffective interventions. Six percent of effective and 33% of ineffective intervention session durations were <5 min, and 80% of effective and 50% of ineffective interventions’ sessions lasted ≥5 min; duration was unspecified in the remaining 11 interventions. Among 5 min or longer interventions, 30% of effective and 17% of ineffective ones were 5–10 min, 19% of effective and 17% of ineffective ones were 11–20 min, and 31% of effective and 17% of ineffective ones were >20 min. Six percent of effective and zero ineffective interventions were combined group and individual, and 6% of effective and 11% of ineffective interventions did not report group versus individual implementation. At-home practice was included in 35% of effective and 17% of ineffective interventions.

Intervention effectiveness was significantly associated with the following parameters: breath pace ($p = 0.01$); use of human-guided training ($p < 0.001$); number of human-guided sessions ($p < 0.001$); among device-guided interventions, use of human-guided training ($p = 0.025$); number of sessions ($p < 0.001$); long-term practice ($p = 0.005$); intervention duration ($p < 0.001$); and session duration <5 versus ≥5 min ($p = 0.005$). Effectiveness was no longer associated with breath pace when considering any pace besides fast-only ($p = 0.10$) or when comparing fast-only to any other pace ($p = 0.06$). All three human-guided training parameters were subsumed into the broader category of human-guided training, as were all three intervention duration measures into long-term practice. Thus, five main parameters were identified as components associated with stress reduction effectiveness, which were subdivided into exclusionary and core components. Breath pace and session duration comprised exclusionary components, in which avoiding fast-only practices and sessions <5 min appears conducive to but not sufficient for intervention effectiveness, while incorporating the core components of human-guided training, multiple sessions, and long-term practice actively contributes to stress reduction benefits.

Figure 4.4 shows the numbers of effective and ineffective interventions by breath pace. Figure 4.5 shows how effective and ineffective interventions were distributed by population (Figure 4.5A) and by use of human-guided training, multiple sessions, and long-term practice, both overall (Figure 4.5B–D) and by population (Figure 4.5E–G).

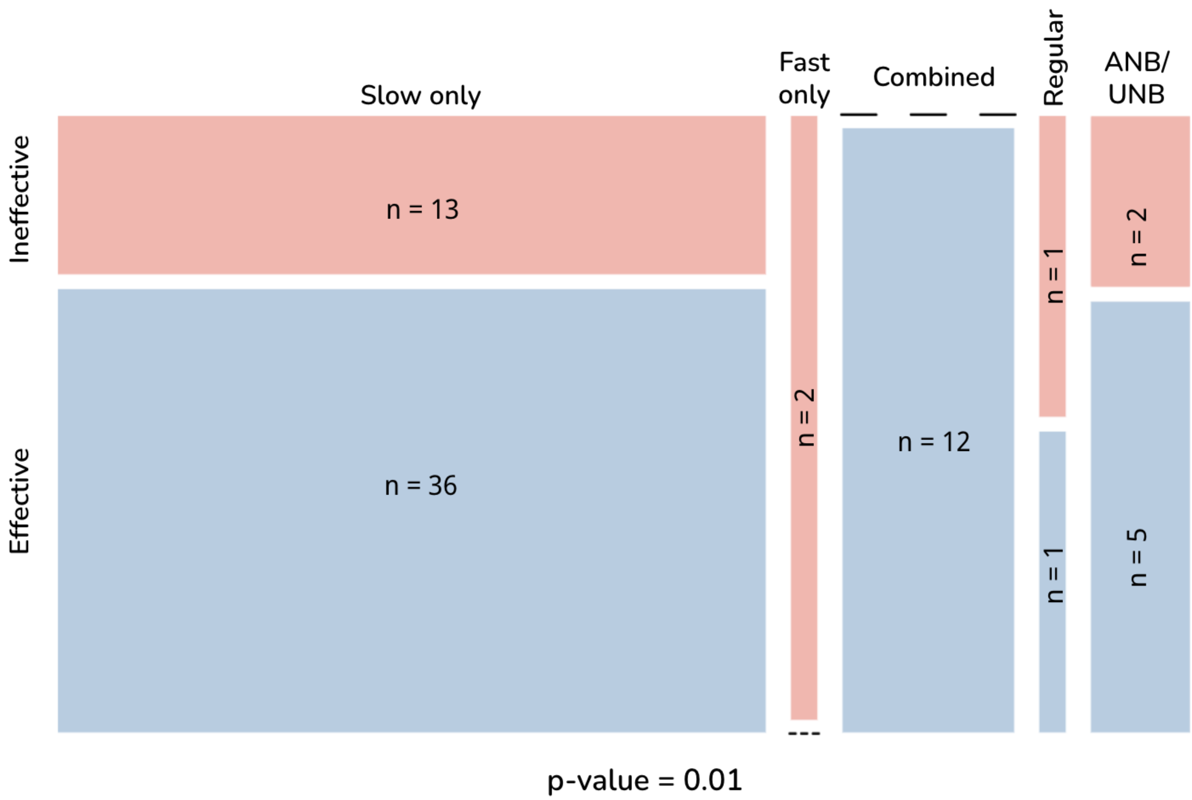

Figure 4.4: Effective and ineffective interventions by breath practice pace. Effective and ineffective interventions by breath practice pace. Blue shaded portion in each category column represents the proportion of effective interventions; red shaded portions reflect ineffective interventions. *p*-value calculated with Fisher's exact test. Breath intervention types defined as fast, breath pace >20 bpm; slow, <12 bpm; regular, 12–20 bpm; combined, fast, and slow breathing with or without ANB/UNB; and ANB/UNB. ANB, alternate-nostril breathing; n, number of interventions; UNB, unilateral nostril breathing.

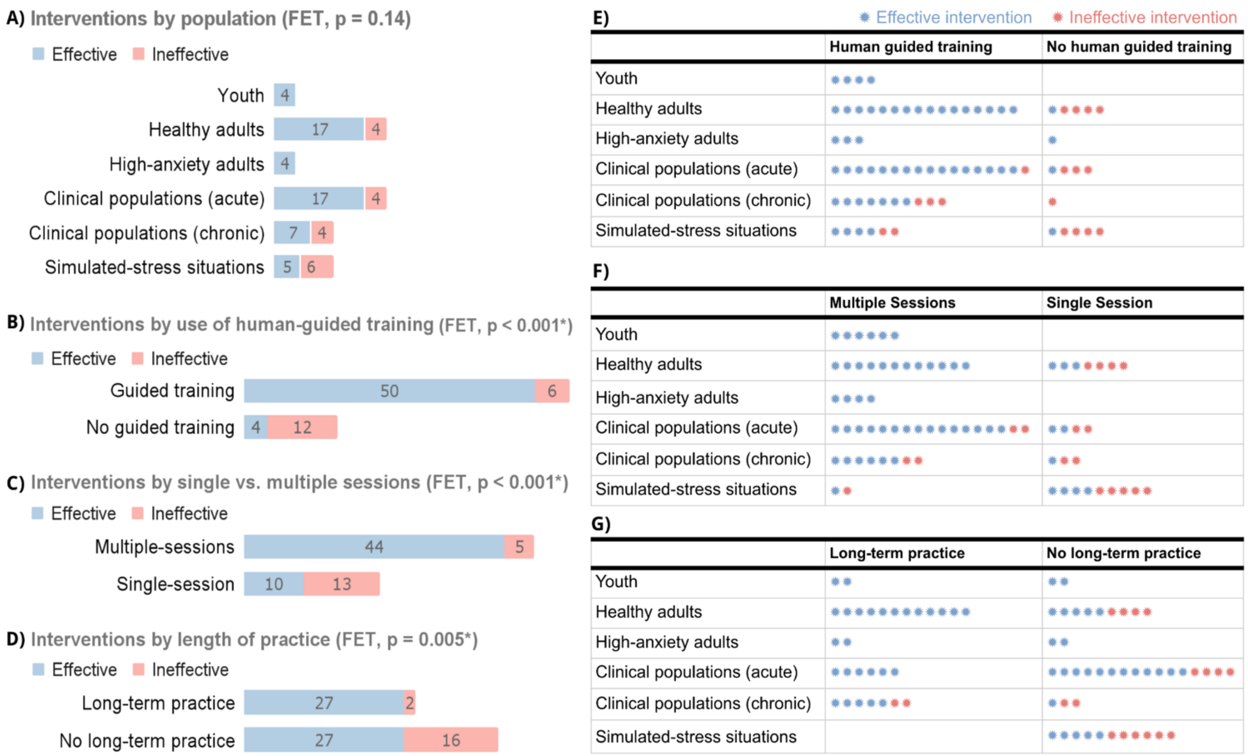

Figure 4.5(A-G): Effective and ineffective breath interventions by population and use of human-guided training, single or multiple sessions, and long-term practice. Each panel is collectively exhaustive of all 72 interventions from 58 studies in total. Numbers in bar graphs of panels (A–D) represent numbers of interventions. Each colored asterisk in panels (E–G) represents one study. Blue bars and asterisks represent effective interventions; pink ones represent ineffective interventions. Human-guided training defined as use of live or pre-recorded audio or video human instruction throughout at least the initial breath session. Multiple sessions defined as performing breathing practice more than once. Long-term practice defined as performing ≥6 sessions over ≥1 week. (A, E–G) Interventions were divided into six broad population categories: youth (n = 4); healthy adults (n = 21); high-anxiety adults (n = 4); clinical, chronic (n = 11); clinical, acute (n = 21); and individuals placed in simulated-stress situations (n = 11). FET, Fisher's Exact Test. * *Statistically significant at p < 0.05.*

Overall, 44 of the 54 effective and 10 of the 18 ineffective interventions incorporated some form of human-guided training during participants' initial breath practice session (Figure 4.5B), with a total number of human-guided sessions ranging from 1 to 40. These sessions ranged from 3 to 60 min among effective interventions and from 3 to 45 min among ineffective ones. Fifty of the 54 effective and 1 of the 18 ineffective interventions incorporated multiple breath practice sessions throughout the intervention (Figure 4.5C), with up to 100+ sessions incorporated. Long-term practice was incorporated in 27 of the effective and 2 of the ineffective interventions (Figure 4.5D), ranging from 1 week to 3 months of practice.

Considering each population specifically, interventions in youth and high-anxiety adults were always effective (Figure 4.5A, E). All eight of these interventions incorporated at least one of the tree core components of human-guided training, multiple sessions, and long-term practice; and none used fast-only or <5 min practices. In healthy adults, all seventeen effective interventions incorporated at least one core component, and all four ineffective ones used zero core components and <5 min sessions. The effective interventions in clinical and simulated-stress populations always used at least one core component; three used <5 min sessions. Among the fourteen ineffective interventions within those populations, seven used one or more core components; of these seven, one used <5 min sessions, and another used both fast-only and <5 min practices.

Synthesis outliers were defined as effective interventions that did not incorporate any of the three core components or ineffective interventions that avoided both fast-only breathing and sessions <5 min and incorporated at least one core component. Six outlier interventions were identified and explored to determine explanatory variables that may be considered potential model caveats (Table 4.3). One intervention was effective despite not incorporating human-guided training, multiple sessions, or long-term practice (Schlatter et al. 2022). Effectiveness may relate to the investigator's presence throughout the device-guided practice, which may have led to unplanned human guidance that was not reflected in the study report. It is also possible that the highly educated and physiologically trained 5th-year medical residents who participated in this study easily adapted to learning a breath practice.

Table 4.3: Outlier interventions with explanatory practice and research caveats.

Intervention		Potential Caveats	
Author, Year (Population)	Description	Practice	Research
Effective practices incorporating zero core components			
Schlatter 2022 (healthy adults)	5 min of 6 bpm relaxing breathing prior to simulated medical scenario and test	• Investigator present during device-guided practice • Physiologically trained residents	
Ineffective practices that incorporated			
Human-guided training			
Meier 2020 (simulated stress)	30 min guided standing relaxation breathing prior to simulated stress test	• Standing still • Interrupted practice	
Human-guided training, multiple sessions			
Kamath 2017 (simulated stress)	15 min guided ANB prior to simulated public speaking task	• Highly technical practice • ANB task performance effects may attenuate stress-reducing effects	
Ratcliff 2019 (clinical, acute)	Guided diaphragmatic breathing for 10 min prior to and during breast biopsy	• Difficult to execute lying on stomach and remaining still for biopsy	• Practice guides not blinded
Human-guided training, multiple sessions, long-term practice			
Thomas 2017 (clinical, chronic)	Guided diaphragmatic breathing with breath holds, guided via DVD		• Practices not continued through outcome period • Outcomes reported at baseline and 12 mo
	Same as above, delivered by physiotherapist		

Outliers defined as effective interventions that incorporated zero core components and ineffective interventions that incorporated ≥1 core component and satisfied both exclusionary components (e.g., avoided both fast-only breathing and sessions <5 min). Caveats report breath practice and study-specific research characteristics that may have increased interventions' stress-reducing effects in effective outlier interventions and those that may have lessened or diluted these effects in ineffective outlier interventions. ANB, alternate-nostril breathing; bpm, breaths per minute; DVD, digital versatile disc; min, minutes; mo, months; w/o, without.

Five interventions were ineffective despite avoiding fast-only and <5 min practices and incorporating at least one core component (Table 4.3). In Meier (2020), the fact that participants were standing still for a 30 min practice and were repeatedly interrupted for stress surveys likely explains the lack of effectiveness. The ANB intervention in Kamath (2017) was ineffective despite incorporating both human-guided training and multiple sessions. Of the three other ANB interventions used in simulated stress situations, the one effective intervention (Sharma et al. 2022) incorporated human-guided training among a population with prior yoga breathing experience. The two ineffective ones had either human-guided training in a yoga-naive population (Kamath et al. 2017) or no such training in a yoga-breathing-experienced population (Telles et al. 2019). All other ANB studies were effective in reducing stress and incorporated ≥2 of the three core components. It may be that in a highly technical practice such as ANB, multiple sessions or prior experience plus human-guided training are required for stress-reducing effects.

In Ratcliff (2019), effectiveness may have been diluted by the difficulty of doing diaphragmatic breathing while lying still and face-down on a procedure table during a breast biopsy. Investigator bias may also have influenced effectiveness, with unblinded investigators leading this active control practice. In Thomas (2017), the practice was not continued by many participants for the entire 12-month measurement window.

Framework Development

Synthesis results were used to develop a conceptual framework of components associated with effective stress reduction breathing interventions (Figure 4.6): avoiding fast-only breathing and session durations <5 min; and including human-guided training, multiple sessions, and/or long-term practice. The framework also identifies caveats reflecting factors that may potentially reduce intervention effectiveness, such as extensive standing, repeated interruptions, involuntarily restricted diaphragmatic expansion, and inadequate training for highly technical practices. Intervention effectiveness may also be impeded in studies that lack blinded practice guides, accountability for at-home practices, and practice continued throughout measurement periods.

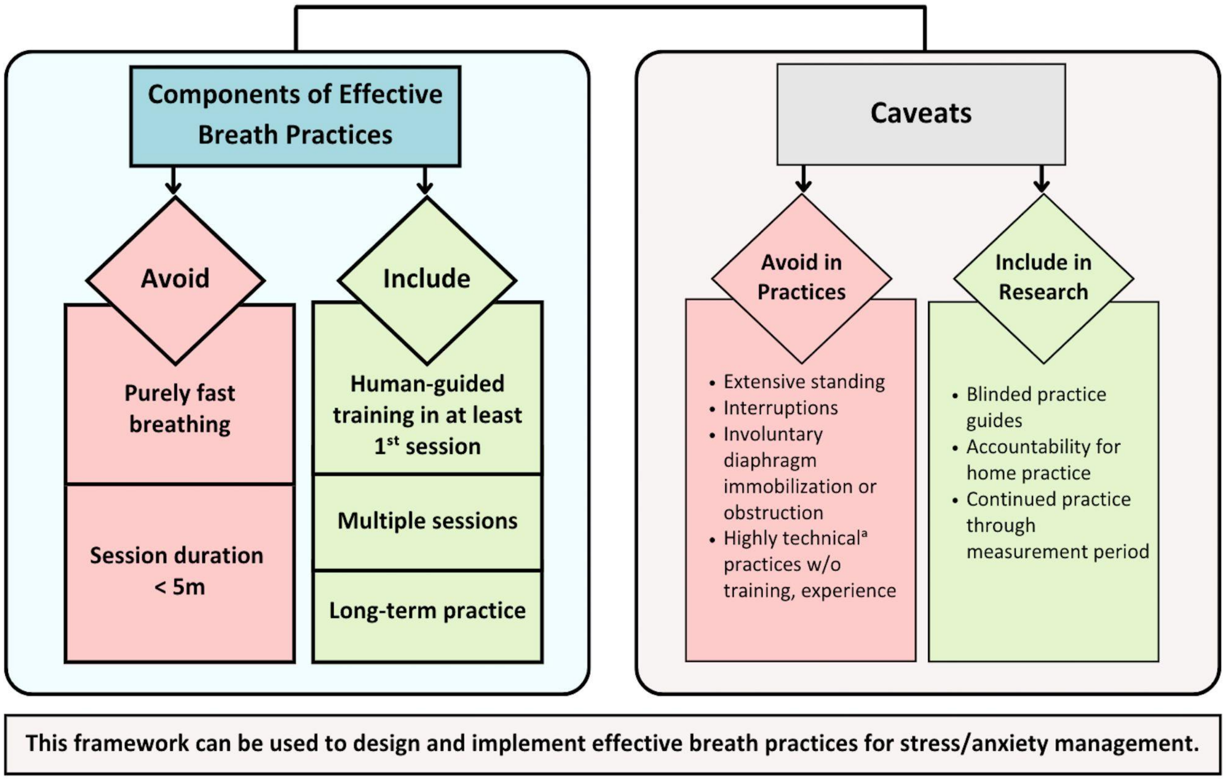

Figure 4.6: Conceptual framework of effective stress reduction breath practices. Based on analysis of 58 studies with 72 total interventions. Components in left-hand box were significantly associated with effectiveness. Caveats describe factors that may impact intervention effectiveness regardless of component inclusion. Human-guided training defined as use of live or pre-recorded audio or video human instruction throughout at least the initial breath session. Multiple sessions defined as performing breathing practice more than once. Long-term practice defined as performing ≥6 sessions over ≥1 week. [a] Highly technical includes breath pace far from regular pace, e.g., extremely fast or extremely slow, or ANB, UNB. ANB, alternate-nostril breathing; UNB, unilateral nostril breathing; vs., versus; w/o, without.

Discussion

Overview

We reviewed the peer-reviewed published literature to evaluate practice components associated with stress reduction effectiveness. We identified 58 clinical studies, comprising 41 RCTs and 17 single-arm, pre-post, non-randomized trials; 5407 total participants were included, with a mean age of 35.9 years and 43.92% female. Among the 72 included interventions, breathing practices significantly reduced stress/anxiety in 54 interventions. Findings were used to develop a conceptual framework of breath practice effectiveness, specifying that stress-reducing interventions incorporated five components: avoidance of fast-only breathing and sessions <5 min; and inclusion of human-guided training, multiple sessions, and/or long-term practice. Neither the population doing the practice, other breath paces besides fast-only, session duration beyond 5 min, group versus individual practice, nor setting were associated with effectiveness.

Breathing practices have become an increasingly popular stress reduction tool with widespread benefits for mental health. A simple PubMed search of “breathing practices” yields 18,721 results, over half of which have been published since 2010. Mobile applications are bringing breathwork to broader audiences, with the number of existing breath apps in the double digits. Despite this popularity, not everyone is aware of the benefits of breathwork; among those who are, emphasis is often placed on specific practice types and durations. Though many breath coaches pride themselves in providing the “best” practice, no singular effective protocol has been established and supported by scientific analyses.

Previous reviews have provided insight into the psychological and/or physiological benefits of slow breathing (Zaccaro et al. 2018), diaphragmatic breathing (Hopper et al. 2019), ANB (Rung et al. 2021), and other breath practices (Malviya et al. 2022; Banushi et al. 2023; Fincham et al. 2023; Miri et al. 2023). While these studies have examined a range of populations, their selection criteria have precluded more nuanced analyses. Although the analysis by Fincham and colleagues attempted to investigate subgroup effects, they included only 12 studies (Fincham et al. 2023). In addition, most reviews include breathing interventions incorporating biofeedback (Zaccaro et al. 2018; Malviya et al. 2022; Banushi et al. 2023; Fincham et al. 2023), which is not readily applicable to at-home practice. Ours is the first work of its kind to disentangle among varied populations the components of isolated breathing interventions that contribute to stress and anxiety reduction from those that do not. The framework provides clear, specific recommendations for individuals implementing their own practices, professionals developing and leading stress reduction programs, and researchers studying the effects of breath practices on stress outcomes.

Exclusionary Components

Breath Pace

Intervention effectiveness was less likely during fast-only breathing versus any other pace, consistent with other reviews finding benefits associated with slow-paced breathing practices (Banushi et al. 2023; Fincham et al. 2023). Polyvagal (Porges 2009) and neurovisceral integration (Thayer and Lane 2000) theories favor slow over fast breathing due to its activation of the parasympathetic nervous system and accompanying effects on the mind and brain (Zaccaro et al. 2018). Our analysis further suggests that, provided fast-only practices are avoided, specific breath pace may not matter, as effectiveness was not associated with pace when fast-only practices were excluded.

Interestingly, fast breathing can successfully reduce stress when paired with slower paces or holds, as seen in the 12 fast + slow interventions, all of which were effective. Such practices may provide benefits by teaching practitioners to slow their breathing patterns and self-soothe during stressful situations; or by building CO_2 tolerance, which is inversely related to symptoms of stress and anxiety (Battaglia et al. 2014). They may, alternatively, train the autonomic nervous system to engage the parasympathetic branch more readily following high sympathetic activation (Brown and Gerbarg 2005). Yet another interpretation resides in the connection between breathing patterns and the brain's neural circuitry, whereby shifting breathing patterns may correspondingly shift neural circuit dynamics and thus mood and mental state (Ashhad et al. 2022).

If this explanation holds true, regular-paced breathing practices would provide no such benefit. Because only two interventions met our 12–20 bpm regular-paced breathing definition, we cannot definitively assess the stress-reducing effects of regulated breathing at one's normal pace. Of the two regular-paced interventions, one was ineffective, which may relate to its lack of framework adherence (Holmes et al. 1978). The other was effective, possibly due to human-guided training and its 12 bpm pace, which may have been slow enough to engender benefits (Conlon et al. 2022).

The lack of effectiveness observed among fast-only breathing interventions should be interpreted with caution, given their underrepresentation in our analyses. The two fast-only interventions either lacked framework adherence (Sakakibara and Hayano 1996) or incorporated poor study design (Watson et al. 2022). Should breathwork's benefits relate to respiration-induced neural entrainment, any breathing pace different from one's usual pattern may offer stress relief—even fast-only practices. Fast breathing could hypothetically reduce stress by acting as an acute stressor that builds resilience over time or by providing a sense of control from learning to regulate one's own breathing and internal state.

Session Duration

The significant association between intervention effectiveness and session duration was driven by interventions using sessions <5 min, six of nine of which were ineffective. Among these, however, four incorporated no core component, and the remaining two included other factors that may have influenced effectiveness. Regarding the latter, stress reduction may have also been hindered by fast-only breathing in Watson and colleague's intervention and by the discomfort of doing deep diaphragmatic breathing after abdominal surgery in Aktas and colleagues' intervention (Watson et al. 2022; Aktaş and İlgin 2023). The presence of core components in the three effective interventions (McCaul et al. 1979; Watson et al. 2022; Aktaş and İlgin 2023) suggests that such short sessions may be particularly sensitive to practice implementation, such that human guidance, multiple sessions, or long-term practice are required for effective stress reduction.

The lack of significant association between effectiveness and session durations ≥5 min indicates that any session duration beyond 5 min can be effective. While no other studies have assessed differences in breath practice effectiveness due to session length, many generally assume a dose-response relationship in which longer sessions are inherently better. Our findings indicate that simply engaging in a breathing practice provides benefits, with sessions as short as 5 min yielding comparable benefits to longer sessions. Interestingly, a recent review by Strohmaier and colleagues reported similar findings about mindfulness-based programs, with larger doses of mindfulness practices no more effective than smaller ones (Strohmaier 2020).

Core Components

Human-Guided Training

The association between human-guided training during initial sessions and effectiveness highlights the value of proper breath mechanics, diaphragmatic engagement, and the ability to control breath pace. Hearing real-time instructions allows participants to receive performance cues and, in the case of live guidance, to ask questions and/or get feedback. Such guidance may enhance adherence and stress reduction outcomes. The fact that this training could be live or pre-recorded and as minimal as one 5 min session implies accessibility to broad populations, although it is notable that all effective interventions among high-anxiety populations included two or more human-guided sessions.

While important, human-guided training does not guarantee stress reduction benefits, and the lack thereof does not prevent effectiveness. Effectiveness may be compromised despite human guidance in the presence of clinical-related breathing restrictions, fast-only or highly technical breathing techniques, and prolonged latency between intervention and outcome measurements. More human guidance may be needed in situations of clinical stress, such as undergoing a breast biopsy (Ratcliff et al. 2019), for learning more technical practices, such as ANB and UNB, or for high-anxiety populations. In some cases, lack of human-guided training may be made up for by multiple sessions that allow participants to learn these nuances themselves over time. Of the four effective interventions that lacked such training, three included multiple sessions (McCaul et al. 1979; Clark and Hirschman 1990; Aktaş and İlgin 2023), and the other (Schlatter et al. 2022) may have incorporated some unreported and unintentional human guidance due to the investigator's presence during the practice.

Multiple Sessions

The observed importance of multiple sessions likely relates to greater practice familiarity and consistency. Multiple sessions took various forms, ranging from two guided individual sessions in one day (Bargale et al. 2021) to five group sessions over 9 months alongside twice-daily at-home practice (Sundram et al. 2014). Intervention effectiveness persisted despite such heterogeneity.

Although 41 of the 44 effective multi-session interventions included at least one human-guided session, having multiple sessions alone appears to support breath practice effectiveness. Three of the four effective unguided interventions included multiple sessions (McCaul et al. 1979; Clark and Hirschman 1990; Aktaş and İlgin 2023); and significant associations between effectiveness, intervention duration, and number of sessions suggest that breathing practices are more beneficial when performed repeatedly. Nevertheless, some single-session interventions were, in fact, effective, with 10 of 23 providing stress reduction benefits. Nine of these 10 were human-guided, suggesting that adequate training may, in some cases, make up for multiple sessions in breath practice efficacy.

Examining the four multi-session interventions that lacked human guidance also suggests that interventions without human-guided training are more likely to be effective when they include simple, easy-to-follow breathing practices alongside device guidance. Interestingly, seven of eight single-session interventions with such simple, device-guided practices were ineffective, highlighting the importance of multiple sessions when human guidance is lacking.

Long-Term Practice

Practicing for a minimum of six sessions over at least a week was significantly associated with effectiveness, suggesting that breathing practices are more likely to confer stress-reducing benefits when performed regularly over time. As with many behaviors, consistent practice is often key to effective skill learning and adaptation. Although these results contrast with other findings of no treatment duration effect (Leyro et al. 2021; Fincham et al. 2023), those reviews may have been limited by small samples, study heterogeneity, and exclusion of human-guided training, which may interact with long-term practice.

All long-term interventions in our review also incorporated human-guided training, suggesting that human-guided training may underlie the association we found between long-term practice and effectiveness. However, examining the relationship further suggests otherwise: 6 of the 27 effective interventions with long-term practice had only one human-guided session, with the remaining sessions performed at home, unguided. If human-guided training were solely responsible for intervention effectiveness, these interventions likely would not have demonstrated benefits, as their outcome measures were taken up to 45 days after human-guided training (Sellakumar 2015). It is more likely that long-term practice enhances intervention effectiveness when coupled with at least one human-guided session, which may help teach novice practitioners proper technique.

Components Not Associated with Effectiveness

Our analysis found no association between effectiveness and study population. Because breathing acts directly on the autonomic nervous system as a "bottom-up" approach to stress reduction (Lehrer et al. 1999; Driscoll and Dicicco 2000; Abelson et al. 2010; Fiorentini et al. 2013; Kromenacker et al. 2018; Li et al. 2018), its benefits likely persist across diverse populations. This finding contrasts with those from Fincham and colleagues, whose review reported a significant benefit of breathwork on stress in non-clinical populations only (Fincham et al. 2023). However, their analysis may have been underpowered with only one intervention in mental health populations; and another recent meta-analysis found significant effects in both psychiatric and healthy populations (Leyro et al. 2021).

It Is worth noting that all interventions in youth and high-anxiety populations were effective. Perhaps this is a coincidence due to the small sample sizes of four interventions each or due to the prevalence of human-guided training and multiple sessions in these interventions. These two core components may alone be a golden ticket to effective stress reduction with breathing practices. Of the 45 interventions in any population that incorporated both of these components, only four were ineffective (Kamath et al. 2017; Thomas et al. 2017; Ratcliff et al. 2019), but this was likely due to taxing clinical situations (Ratcliff et al. 2019), inadequate training or experience for a more technical practice (Kamath et al. 2017), and practice discontinuation (Thomas et al. 2017). Alternatively, the effects of breathwork may be more potent in high-anxiety populations and youth. The respiratory dysregulation and high chronic stress accompanying anxiety disorders may augment sensitivity to breath practice interventions (Paulus 2013). Accustomed to being in learning environments, youth may easily catch on to these practices with human guidance, and their developing nervous systems may be highly receptive to interventions (Griffin 2017).

We found that interventions given to groups were equally effective as those given to individuals, a finding corroborated by other recent literature (Fincham et al. 2023). However, given the small number of group interventions in high-anxiety and acute chronic populations, it is possible that populations with particularly dysregulated breathing (Grossman 1983; Masaoka and Homma 1997; Wilhelm et al. 2001) may fare better with one-on-one attention.

Interventions with multiple at-home practice sessions were equally as effective as those with multiple sessions administered via human guidance. Thus, human-guided training does not appear necessary beyond the first session, after which breathing practices can be carried out individually at home. Nonetheless, interventions incorporating at-home practices should motivate and assess practice compliance, as our three ineffective interventions with at-home practice (Thomas et al. 2017; Aktaş and İlgin 2023) reported either inconsistent or unknown practice compliance.

Framework Caveats

By scrutinizing the six outlier interventions, we identified framework caveats that may either improve or undermine effectiveness, independent of the proposed framework components. Regarding the former, our analysis indicates that even breathing practices that diverge slightly more from one's spontaneous pattern may not require human-guided training, given adequate device guidance paired with strong accountability and physiologically trained participants. While Schlatter and colleagues' effective intervention (Schlatter et al. 2022) lacked human guidance, their 6 bpm practice among 5th-year medical residents was guided via a screen cursor with an investigator present to ensure practice adherence.

On the physical side, breath practices should be performed in a comfortable position without prolonged standing or involuntary diaphragmatic immobilization. The 30 min of standing during Meier and colleagues' human-guided intervention may have caused discomfort and interfered with potential benefits (Meier et al. 2021); though perhaps shorter standing practice durations would be effective. Deep or diaphragmatic breathing may provide minimal benefit when voluntary full diaphragmatic movement is lacking, such as during a breast biopsy (Ratcliff et al. 2019). Practices placing less emphasis on the diaphragm and more emphasis on breath cadence, such as extended exhale or general slow breathing, may offer better relief in such situations.

Breath practices may also be less likely to reduce stress when they include interruptions. While practicing breathing in a standing position may have influenced Meier's findings, so could its repeated data collection interruptions, which may have reduced focus and induced sufficient stress to negate benefits.

Analysis of included ANB/UNB interventions suggests that more technical practices may require extra training or experience. One ANB intervention was ineffective despite fitting our framework, incorporating a single human-guided session among yoga-naive participants (Kamath et al. 2017). Of our four effective ANB/UNB interventions carried out in novice practitioners, all included human-guided training for a minimum of four sessions (Gupta et al. 2010; Marshall et al. 2014; Naik et al. 2018; Chandrababu et al. 2019). These findings are consistent with ANB's stress-reducing effects reported elsewhere, in which all included interventions incorporated long-term practice alongside human-guided training (Rung et al. 2021). Nonetheless, an effective human-guided but short-term intervention among individuals with prior ANB or yoga breathing experience suggests that single-session ANB may confer benefits when carried out among experienced practitioners and with human-guided training (Sharma et al. 2022). The technical nature of learning and practicing ANB may initially attenuate its stress-reducing effects, specifically for inexperienced practitioners, until repeated practice occurs. Conversely, human-guided training and long-term practice may not be necessary for exceedingly simple breathing practices, such as those at a slightly slower-than-normal pace (e.g., 10 or 8 bpm) that may be more accessible to breathwork-naive individuals (McCaul et al. 1979; Clark and Hirschman 1990).

Our findings also suggest that long-term effectiveness requires long-term compliance. Participants in Thomas and colleagues' 2017 ineffective interventions engaged in regular practice for 6 to 8 weeks but were not practicing most days by the time of the 12-month stress measurement (Thomas et al. 2017). Another review found that breathwork benefits may persist for a brief period after practice ends, although practice adherence was not assessed in that study (Fincham et al. 2023). In our analysis, all other studies with long-term measurements included either regular guided practice throughout or specific instructions and motivation for at-home practice.

Limitations and Future Directions

Findings from this analysis must be considered in light of its potential limitations. Due to the mediocre-at-best methodological quality of included studies, some effectiveness findings may not be as reliable or valid as assumed. Future research should reduce potential bias by incorporating appropriate blinding and measurements, intention-to-treat analyses, concealed treatment allocation, and larger sample sizes. The articles included in our analysis demonstrated wide heterogeneity in reporting practice and implementation details, often omitting key data relevant to our framework. Zaccaro and colleagues propose a checklist of data points to include in breath studies (Zaccaro et al. 2018), including factors such as breath pace, inspiration/expiration ratio, pauses/holds duration, and others. Studies should also report on implementation components, such as human-guided training, number of sessions, practice compliance, session durations, group-versus-individual practice, etc. In the comparative studies included in this review, lack of active controls may have biased results with placebo effects. Future research should compare breath practices with other self-care interventions that are framed as helping with stress reduction.

Although we aimed to address breathing practices performed in isolation and accessible to broad populations, results may have differed if we had included those combined with other practices such as yoga, meditation, or biofeedback. For example, HRV is a well-established stress measure (Kim et al. 2018). Changes in self-reported stress may differ when participants see HRV responses and modify their breath pace to achieve certain HRV outcomes. More research is needed comparing biofeedback-enabled breath practices with breath practices alone to help disentangle the cause-and-effect relationships between breath practices, HRV, and stress. Physiological outcomes were also not considered in our analysis. While these outcomes are helpful for understanding breathing practices' mechanisms of action, our goal was to develop a framework for practical application, regardless of the mechanism of action.

The framework presented here is based on associations between breath practice components and effectiveness; it does not necessarily represent causal relationships. A meta-analysis that pools all data into one larger analysis was not conducted due to heterogeneity in populations, breath practice details, outcome metrics, and statistical approaches in included studies. While existing meta-analyses provide valuable insights (Leyro et al. 2021; Laborde et al. 2022; Fincham et al. 2023), we included a broader array of studies to establish a deeper understanding of how various practice and implementation factors are associated with stress reduction.

Although our results suggest that any breath pace besides fast-only can be effective when the framework criteria are applied, there may be finer distinctions among populations and specific outcomes of interest in which different practices help specific populations in different ways. More carefully controlled and methodologically rigorous experiments may reveal whether these more nuanced distinctions exist.

The potential caveats identified in this framework are hypotheses based on data available in outlier interventions; it could be that other factors drove effectiveness in these interventions. Only two databases were searched for this systematic review; however, the large number of identified and included studies lends credence to the conclusions presented. Lastly, caution is warranted in applying these results to individuals with certain clinical conditions, such as epilepsy, heart conditions, or pregnancy, whose reactions to intense practices may vary.

Implications

We have identified simple yet important criteria for learning and implementing breath practices for effective stress reduction. Our research demonstrates that the important factors to consider when implementing breath practices for stress reduction are avoiding fast-only and <5 min practices and incorporating appropriate training and continued practice. Extensive standing, interruptions, involuntarily restricted diaphragmatic movement, and inadequate training for highly technical practices may render otherwise promising interventions ineffective. Besides these factors, practitioners and program developers can be less concerned with the specific details of a breath practice, such as finer distinctions in pacing, durations beyond 5 min, group or individual practice, and setting. While these still need to be considered in implementing any breath practice, our findings indicate that over-emphasis on these details is unwarranted and a misdirected placement of focus.

This knowledge can and should provide a sense of freedom for individual practitioners and program developers alike in tailoring programs to meet their needs for stress reduction effectiveness. While many people may benefit from a simple breath practice, some may be reluctant to start for fear of doing the "wrong method." Our results not only support the broad-ranging benefits of a variety of simple breathing techniques but also provide comfort in the knowledge that, as long as this simple framework is followed, other details are less important for maximizing stress reduction benefits of breathing practices. Specific practices to consider include extended exhale breathing, box breathing, slow breathing with pauses/holds, slow diaphragmatic breathing, combined fast + slower breathing practices, and ANB/UNB. Both initial training sessions and ongoing practice sessions can be as short as 5 min. Breath practice programs should incorporate initial human-guided training and be clear about the specific long-term practice criteria for success.

Future breath practice studies should incorporate rigorous data collection and report breath practice implementation details to allow for analysis of finer practice distinctions and this framework's validity. Real-time guidance in these studies should be carried out by individuals blinded to experimental conditions, and practices should continue throughout the measurement period. Accountability for, motivation for, and assessment of practice compliance should be addressed, especially for home practices and longer-term follow-up periods. Until more such research is conducted, following the framework results from this analysis will improve stress management effects associated with breathing practices.

Actionable Takeaways

Following the below framework criteria will increase the likelihood of beneficial stress outcomes associated with breath practices (Table 4.4).

Table 4.4.4: Actionable takeaways.

For Practitioners, Program Developers, and Leaders Designing and Implementing Breath Practices	For Researchers Designing and Implementing Breath Practice Studies
● Pace: ○ Choose any breath pace that incorporates some form of regulated slow breathing, such as: ▪ extended exhales; box breathing; slow breathing with pauses/holds; slow diaphragmatic breathing; combined fast+slower breathing; ANB/UNB ○ Avoid practices involving fast breathing alone ● Training: ○ For at least the 1st session, follow human-voice guidance ○ This can be in-person or via live or recorded video/audio ○ It can be as short as 5 minutes ○ Get extra training if doing ANB/UNB for the first time ● Setup: ○ Be in a comfortable seated or lying down position ○ Avoid extensive standing ○ Have access to free diaphragmatic movement ○ Be in a place where you will not be interrupted ● Practice: ○ Avoid practices shorter than 5 minutes ○ Do it more than once ○ Keep doing it for continued benefit	● Breath practice design: Follow the practice tips in left-hand column ● Study design: ○ For real-time practice guidance, use instructors or guides who are blinded to experimental condition ○ Create accountability for, motivate, and assess practice compliance, especially for: ■ home practices ■ longer-term follow-up periods ○ Ensure that practices are continued throughout outcome measurement periods

Extended exhale breathing defined as a breath pattern in which the exhale is longer than the inhale; box breathing defined as breathing with equal durations of inhales, post-inhale holds, exhales, and post-exhale holds. ANB, alternate-nostril breathing; UNB, unilateral nostril breathing.

Conclusion

We developed an evidence-based framework for effectively implementing stress reduction breath practices. Despite prior knowledge that breathing practices support stress reduction, how these effects vary across populations, breath practice types, and implementation approaches remained unclear. While commonly emphasized factors such as specific breath pace, population, and group versus individual practice were not found to be associated with effectiveness, five core components were: avoiding fast-only and <5 min practices; and incorporating human-guided training during initial sessions, multiple sessions, and long-term practice. Following this simple, evidence-based framework can help maximize the stress reduction benefits of breathing practices among broad populations.

Acknowledgements

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Appendix

PubMed and ScienceDirect Search Details

PubMed keywords: anxiety, stress, panic, breath, breathing, breathwork, respiration, respiratory, pranayama, inspiratory, expiratory, and diaphragmatic.

PubMed MeSH terms [“OR” between all]:

Anxiety/analysis
Anxiety/etiology
Anxiety/pathology
Anxiety/physiology
Anxiety/physiopathology
Anxiety/rehabilitation
Anxiety/therapy
Stress, Psychological/analysis
Stress, Psychological/physiology
Stress, Psychological/physiopathology
Stress, Psychological/prevention, and control
Stress, Psychological/psychology
Stress, Psychological/rehabilitation
Stress, Psychological/therapy
panic
panic/physiology
panic/prevention and control
panic/therapy
panic disorder/etiology
panic disorder/physiology
panic disorder/physiopathology
panic disorder/prevention and control
panic disorder/therapy
breathing exercises*
respiration*
Diaphragm/therapy

PubMed Search String:

((((((((((((((“Anxiety/analysis”[Mesh] OR “Anxiety/etiology”[Mesh] OR “Anxiety/pathology”[Mesh] OR “Anxiety/physiology”[Mesh] OR “Anxiety/physiopathology”[Mesh] OR “Anxiety/prevention and control”[Mesh] OR “Anxiety/psychology”[Mesh] OR “Anxiety/rehabilitation”[Mesh] OR “Anxiety/therapy”[Mesh])))) OR (“Stress, Psychological/analysis”[Mesh] OR “Stress, Psychological/education”[Mesh] OR “Stress, Psychological/etiology”[Mesh] OR “Stress, Psychological/pathology”[Mesh] OR “Stress, Psychological/physiology”[Mesh] OR “Stress, Psychological/physiopathology”[Mesh] OR “Stress, Psychological/prevention and control”[Mesh] OR “Stress, Psychological/psychology”[Mesh] OR “Stress, Psychological/rehabilitation”[Mesh] OR “Stress, Psychological/therapy”[Mesh])))) OR ((("panic"[MeSH Terms] OR "panic/physiology"[MeSH Terms] OR "panic/prevention and control"[MeSH Terms] OR "panic/therapy"[MeSH Terms] OR "panic disorder/etiology"[MeSH Terms] OR "panic disorder/physiology"[MeSH Terms] OR "panic disorder/physiopathology"[MeSH Terms] OR "panic disorder/prevention and control"[MeSH Terms] OR "panic disorder/therapy"[MeSH Terms]))))) AND (((("breathing exercises"[MeSH Terms]) OR "respiration"[MeSH Terms])) OR "Diaphragm/therapy"[Mesh])) AND English[lang])) AND English[lang])) OR ((((((anxiety[Title/Abstract] OR stress[Title/Abstract] OR panic[Title/Abstract])) AND English[lang])) AND (((breath[Title/Abstract] OR breathing[Title/Abstract] OR breathwork[Title/Abstract] OR respiration[Title/Abstract] OR respiratory[Title/Abstract] OR pranayama[Title/Abstract] OR inspiratory[Title/Abstract] OR expiratory[Title/Abstract] OR diaphragmatic[Title/Abstract])) AND English[lang])) AND English[lang])

PubMed filters:

English Language

PubMed study types:

clinical trial
clinical study
controlled clinical trial
pragmatic clinical trial
randomized controlled trial

ScienceDirect study types:

Research studies

ScienceDirect title keywords:

("breath" OR "breathwork" OR "pranayama" OR "respiration" OR "respiratory" OR "diaphragmatic") AND ("stress" OR "anxiety" OR "panic").

Data Points Abstracted from Articles Accepted for Review

The following data were collected from each article included in the review:
General Study and Intervention Data Abstraction

- Study (i.e., Timestamp, RefID, Author, Title)
- Is the psychological (e.g., survey-based) stress/anxiety measure the primary outcome?
- Journal
- Year
- Study design (e.g., RCT, non-randomized prospective trial, etc.)
- Inclusion criteria
- Exclusion criteria
- Other population descriptions
- Setting
- Geographic location
- Sample size: Intervention (Intervention)—randomized
- Sample size: Intervention (Intervention)—at baseline
- Sample size: Intervention—# completed

- Sample size: control—randomized
- Sample size: control—at baseline
- Sample size: control—# completed
- Sample size: notes
- % Female: overall
- % Female: Intervention
- % Female: control
- Subgroups considered
- Age: Mean—Overall
- Age: Mean—Intervention
- Age: Mean—control
- Race/ethnicity (% each)
- Intervention type
- Intervention other: parameters, components. etc. (What situations is breath protocol being used?)
- Control description
- Measurement tools: stress/anxiety-related
- Measurement tools: other
- Results: stress/anxiety-related
- Results: other metrics
- Subgroup results
- Limitations
- Implications
- Notes
- CLEAR Score of study quality
- Study population category

Framework Data Abstraction

- Significant Benefit for Stress Outcome (yes/no)
- Intervention: breathing type (i.e., slow, fast, combined fast-slow, other)
- Slow breathing type(s) used
- Describe fast breathing practice (if used)
- Intervention breath pattern
- Breaths per minute (bpm) in breath practice
- Note regarding bpm
- Human-guided training (yes/no)
- Type of human-guided training
- Number of human-guided training sessions
- Number of minutes per human-guided training session
- Device-guided breath training/pacing (yes/no)
- Device type
- Number of device-guided training sessions
- Number of minutes per device-guided training session
- Intervention: group or individual
- Number of group sessions
- Number of minutes per group session
- Intervention homework (yes/no)

- Intervention homework description
- Total number of homework breath sessions
- Length of homework breath sessions (minutes)
- Intervention duration (days)
- Multiple (≥1) sessions (yes/no)
- Number of breath practice sessions, total known
- Length of general sessions (minutes)
- Length of group sessions, if done (minutes)
- Long-term practice (yes/no)
- Sessions continued through outcome measurement (yes/no)
- Control includes (e.g., no control/usual care/no intervention)
- At least one framework criterion met (yes/no)
- Framework: effectiveness of breathing practice
- Which criteria were included
- How many criteria were included
- Randomized controlled trial (yes/no)
- Primary outcome: stress/anxiety (yes/no)
- How many times were stress/anxiety outcomes measured
- Participants: # total randomized

Modified CLEAR-NPT Quality Assessment Tool (Boutron et al. 2005; Chen et al. 2012)

CLEAR-NPT uses a checklist of 10 specific quality assessment criteria regarding blinding, group allocation, care providers' experience/skill, participant adherence, and reporting details to evaluate reports of nonpharmacological treatments. The modified form of the checklist used in this review includes an additional question regarding the comparability of treatment and control groups. Due to the difficulty of blinding in behavioral interventions, the modified form also provides alternative quality assessment questions when blinding is not possible for participants or clinicians. Quality score is calculated by dividing the number of met criteria by the number of applied criteria for a final quality index ranging from 0.0 to 1.0. Because some criteria may not apply to all studies, this approach allows for a more valid comparison across studies.

Supplemental Table 4.1: Modified CLEAR-NPT quality assessment tool questions.

	Criterion	Yes	No	Unclear
1	Was the generation of allocation sequences (group assignment procedure) adequate?			
2	Was the treatment allocation concealed?			
3	Were details of the intervention administered to each group stated or made available?			
4	Were care providers' experience or skills in each arm (group) appropriate?			
5	Was participant adherence or compliance assessed quantitatively?			
6	Were participants adequately blinded? ● If NO, please go to 6.1.1 and 6.1.2. ● If YES, please go to 7			
6.1.1	Were other treatments and care (i.e., co-interventions) the same in each randomized group?			
6.1.2	Were withdrawals and lost-to-follow-up the same in each randomized group?			
7	Were care providers for the participants adequately blinded? ● If NO, please go to 7.1.1 and 7.1.2. ● If YES, please go to 8.			
7.1.1	Were all other treatments and care (co-interventions) the same in each randomized group?			
7.1.2	Were withdrawals and lost-to-follow-up the same in each randomized group?			
8	Were outcome assessors adequately blinded to assess the primary outcomes?			
8.1	If outcome assessors were not adequately blinded, were specific methods used to avoid ascertainment bias (systematic differences in outcome assessment)?			
9	Was the follow-up schedule the same in each group? (parallel design)			
10	Were the treatment and control group comparable at entry? (Any significant differences at baseline?)			
11	Were the main outcomes analyzed according to the intention-to-treat principle?			
Total	Total Scores (number of Yes)			

Quality score = total number of Yes/total number of applied criteria.

National Heart Lung Blood Institute-NHLBI/National Institutes of Health-NIH Quality Assessment Tool (NHLBI 2023) for Pre-Post Studies with No Control Group

This tool provides a qualitative evaluation of studies' internal validity by using questions about the clarity of study objectives, adequacy of the study population and sample size, delivery and description of the intervention, appropriateness of statistical methods, and other metrics. Each study's quality score is based on the total number of "yes" answers divided by total number of questions answered, and that score is used to assign each article with a quality assessment ranking of good, fair, or poor using the same scoring as that used for CLEAR-NPT: <0.6, poor quality; 0.6–0.8 fair; and >0.80 good.

Guidance for using NHLBI-NIH Quality Assessment Tool:

"The questions in the quality assessment tool were designed to help reviewers focus on the key concepts for evaluating the internal validity of a study. They are not intended to create a list from which to add up items to judge a study's quality.

Internal validity is the extent to which the outcome results reported in the study can truly be attributed to the intervention or exposure being evaluated and not to biases, measurement errors, or other confounding factors that may result from flaws in the design or conduct of the study. In other words, what is the ability of the study to draw associative conclusions about the effects of the interventions or exposures on outcomes?

Critical appraisal of a study involves considering the risk of potential for selection bias, information bias, measurement bias, or confounding (the mixture of exposures that one cannot tease out from each other). Examples of confounding include co-interventions, differences at baseline in patient characteristics, and other issues throughout the questions above. A high risk of bias translates to a rating of poor quality; a low risk of bias translates to a rating of good quality. Again, the greater the risk of bias, the lower the quality rating of the study.

In addition, the more attention in the study design to issues that can help determine if there is a causal relationship between the exposure and outcome, the higher quality of the study. These issues include exposures occurring prior to outcomes, evaluation of a dose-response gradient, accuracy of measurement of both exposure and outcome and sufficient timeframe to see an effect.

Generally, when reviewers evaluate a study, they will not see a "fatal flaw" but instead will find some risk of bias. By focusing on the concepts underlying the questions in the quality assessment tool, reviewers should ask themselves about the potential for bias in the study they are critically appraising. For any box checked "no" reviewers should ask, "What is the potential risk of bias resulting from this flaw in study design or execution?" That is, does this factor lead to doubt about the results reported in the study or doubt about the ability of the study to accurately assess an association between the intervention or exposure and the outcome?

The best approach is to think about the questions in the assessment tool and how each one reveals something about the potential for bias in a study. Specific rules are not useful, as each study has specific nuances. In addition, being familiar with the key concepts will help reviewers be more comfortable with critical appraisal. Examples of studies rated good, fair, and poor are useful, but each study must be assessed on its own."

Questions:

1. Was the study question or objective clearly stated?

2. Were eligibility/selection criteria for the study population prespecified and clearly described?
3. Were the participants in the study representative of those who would be eligible for the test/service/intervention in the general or clinical population of interest?
4. Were all eligible participants that met the prespecified entry criteria enrolled?
5. Was the sample size sufficiently large to provide confidence in the findings?
6. Was the test/service/intervention clearly described and delivered consistently across the study population?
7. Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants?
8. Were the people assessing the outcomes blinded to the participants' exposures/interventions?
9. Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis?
10. Did the statistical methods examine changes in outcome measures from before to after the intervention? Were statistical tests carried out that provided p-values for the pre-to-post changes?
11. Were outcome measures of interest taken multiple times before the intervention and multiple times after the intervention (i.e., did they use an interrupted time-series design)?
12. If the intervention was conducted at a group level (e.g., a whole hospital, a community, etc.), did the statistical analysis take into account the use of individual-level data to determine effects at the group level?

Supplemental Table 4.2: Stress/anxiety metrics and outcomes of included studies (N = 58) by population and use of stress/anxiety as the primary or secondary outcome.

Author, Year, Setting	**Stress/Anxiety Metric**	**Outcomes ****	**Quality Score, Tool** † (Boutron et al. 2005; NHLBI 2023)
		A. Youth	
		Youth: Stress/anxiety as primary outcome	
* **Sellakumar 2015** India, secondary school (grades 6–12)	STAI-state, trait	After Ix: • Ix but not C had significant decreases in state and trait anxiety ($p < 0.001$ for both) • These reductions were significantly greater in Ix than in C ($p < 0.001$ for state and trait)	0.44 (CLEAR) Poor
* **Khng 2017** Singapore, 4 elementary schools	STAI-C-state	When doing test after and w/Ix: • Ix had significantly greater anxiety reduction vs. C ($p = 0.02$) • Ix had significantly larger increases in math scores ($p = 0.04$)	0.57 (CLEAR) Poor
* **Bargale et al. 2021** India, hospital pediatric dentistry dept.	Animated emoji scale	• **From before to after anesthetic procedure, significant anxiety decrease in both groups** ($p < 0.001$) w/no significant differences between groups ($p > 0.001$)	0.86 (CLEAR) Good
		Youth: Stress/anxiety as secondary outcome	
* **Hakked et al. 2017** India, swim academy	SAS-2	From before to after Ix: • Ix improved significantly more than C in: max voluntary ventilation ($p = 0.02$); forced vital capacity ($p = 0.026$); swim strokes per breath ($p = 0.002$) • **Ix but not C significantly improved anxiety (p = 0.031)**, concentration ($p = 0.022$), somatic complaints ($p = 0.037$), inspiratory reserve volume ($p < 0.05$), and swim strokes per breath ($p \leq 0.001$)	0.69 (CLEAR) Fair
		B. Healthy Adults	
		Healthy Adults: Stress/anxiety as primary outcome	
* **Gupta et al. 2010** India, yoga training camp	Sinha Anxiety Scale	• From before to after Ix, **significant decrease in mean anxiety** and BDI ($p < 0.01$) ‡‡	0.25 (NHLBI) Poor
* **Bhimani et al. 2011** India, medical college	Authors' 20-item stress questionnaire	From before to after Ix: • Total stress score significantly decreased ($p = 0.0001$) • Low- and high-frequency HRV showed decreased sympathetic and increased parasympathetic influences and improved sympathovagal balance ($p = 0.0001$ all)	0.27 (NHLBI) Poor

Supplemental Table 4.2: Stress/anxiety metrics and outcomes of included studies (N = 58) by population and use of stress/anxiety as the primary or secondary outcome, Continued

Author, Year, Setting	**Stress/Anxiety Metric**	**Outcomes ****	**Quality Score, Tool †** (Boutron et al. 2005; NHLBI 2023)
* **Sharma et al. 2013** India, yoga research center and school	PSS	From baseline to 12 wks: • Significant PSS decrease in Ix-1 and Ix-2 ($p = 0.000$ both) • Significant improvement in cardiovascular measures for Ix-2 ($p < 0.05$) but not Ix-1 ($p > 0.09$)	0.66 (CLEAR) Fair
* **Sundram et al. 2014** Malaysia, automotive assembly plant	DASS-21 stress subscale	9-mo **DASS-21** was significant: • **Reduced** from baseline in Ix and C for all subscales ($p < 0.001$), and this difference was significantly greater in Ix than C for stress subscale ($p < 0.001$) • Differences between Ix and C ($p < 0.001$)	0.62 (NHLBI) Fair
* **Schmalzl et al. 2018** US, university town	PSS	• Following the 8 wk program, significant: **PSS decrease in Ix and C** ($p < 0.01$) • Salivary cortisol decrease in Ix and C ($p < 0.01$) • Improved visual discrimination task in Ix and C ($p = 0.017$) • Improved overall perceptual sensitivity in C ($p < 0.01$) but not Ix ($p > 0.05$)	0.75 (CLEAR) Fair
* **Okado et al. 2020** US, university setting	PSS, GAD-7	From baseline to 2 wks: • **PSS significantly decreased for Ix-1** ($p < 0.01$), Ix-2 ($p < 0.05$), and Ix-3 ($p < 005$), but not C ($p > 0.05$) • GAD-7 significantly decreased for Ix-1 ($p < 0.05$) • PHQ-15 somatization significantly decreased in Ix-2 ($p < 0.05$) and Ix-3 ($p < 0.05$) • PHQ-9-M depression significantly decreased for Ix-1 ($p < 0.01$) and Ix-2 ($p < 0.05$)	0.31 (CLEAR) Poor
* **Magnon et al. 2021** France, setting unclear	SAI	**SAI significantly lower** post-Ix among entire group ($p < 0.001$), young adults ($p = 0.003$), and older adults ($p = 0.019$) • Significant increase in HF power after Ix ($p < 0.001$), which was greater in older adults than younger ($p = 0.042$)	0.67 (NHLBI) Fair
* **Balban et al. 2023** US, remote setting	STAI	• Ix-1, Ix-2, and Ix-3 had significant improvement in mood and lower respiratory rate compared w/C ($p < 0.05$ for all) • **Averaged over 28 days, all groups significantly reduced state anxiety pre- to post-practice** ($p < 0.0001$ all) • No significant change in trait anxiety in any groups, nor differences between groups ($p > 0.05$)	0.53 (CLEAR) Poor

Supplemental Table 4.2: Stress/anxiety metrics and outcomes of included studies (N = 58) by population and use of stress/anxiety as the primary or secondary outcome, Continued

Author, Year, Setting	Stress/Anxiety Metric	Outcomes **	Quality Score, Tool † (Boutron et al. 2005; NHLBI 2023)
Healthy Adults: Stress/anxiety as secondary outcome			
* **Busch et al. 2012** Germany, university setting	POMS tension-anxiety	Following Ix: • **Tension-anxiety significantly improved** in Ix-1 and Ix-2 ($p < 0.0001$) • Ix-1 and Ix-2 significantly improved in depression, anger ($p < 0.01$ all) and total mood disturbances ($p < 0.01$ Ix, $p < 0.05$ Ix-2), and not on vigor, fatigue, or confusion scales ($p > 0.05$ all) • No significantly different between Ix-1 and 2 on any POMS measures ($p = 0.55$) • Ix-1 showed significant increases in pain thresholds ($p < 0.001$) and reductions in sympathetic activity ($p = 0.002$)	0.73 (NHBLI) Fair
Lin et al. 2014 Taiwan, university setting	VAS-anxiety	During Ix: • Significant differences between all Ix's for SDNN ($p < 0.001$), LF ($p < 0.001$), and LF/HF ratio ($p < 0.001$), but not HF ($p = 0.06$) Using retrospective ratings taken after all Ix's: • Significantly greater relaxation for all compared to baseline ($p < 0.05$ all) • **No significant differences in anxiety** between any Ix and baseline ($p > 0.05$ all)	0.58 (NHLBI) Poor
* **Hunt et al. 2018** US, large private university	10-point Likert scale of subjective stress vs. relaxation	• Compared w/C, Ix resulted in significantly higher HRV ($p < 0.001$), lower respiration rate ($p < 0.001$), higher tidal volume ($p = 0.001$), and lower HR ($p < 0.001$) • **Stress was significantly lower after Ix and C** ($p < 0.001$ both) than after paced breathing alone • No significant stress differences after Ix vs. C ($p = 0.14$) • No significant differences between Ix and C in any outcomes during cognitive stressor challenge (p-value not reported)	0.56 (CLEAR) Poor
* **Naik et al. 2018** India, medical school	PSS	After 12 wks, Ix but not C had significant: • Improvements in HR, SBP, DBP ($p < 0.05$), not BMI and WHR ($p > 0.05$) • **Decrease in PSS** ($p < 0.0001$) • Compared to C, Ix had greater PSS decrease ($p < 0.05$)	0.62 (CLEAR) Fair

Supplemental Table 4.2: Stress/anxiety metrics and outcomes of included studies (N = 58) by population and use of stress/anxiety as the primary or secondary outcome, Continued

Author, Year, Setting	**Stress/Anxiety Metric**	• **Outcomes** **	**Quality Score, Tool** † (Boutron et al. 2005; NHLBI 2023)
* **Conlon et al. 2022** UK, University of Bath	IAMS, 7-point Likert scale of perceived stress	• No significant Ix effects on shooting performance (*p* > 0.05) • Post-Ix: • **State anxiety significantly decreased in Ix-1** (*p* < 0.001) **and Ix-2** (*p* = 0.018) but not C (*p* > 0.05) • **Perceived stress significantly decreased in Ix-1** (*p* < 0.001) **and Ix-2** (*p* = 0.016) but not C (*p* > 0.05)	100 (CLEAR) Good
* **Schlatter et al. 2022** France, university medical school	VAS-stress	• Overall performance was significantly greater in Ix-1 (*p* = 0.013) and Ix-2 Ix-2 (*p* = 0.009) vs. C • Clinical performance was significantly greater in Ix-1 (*p* = 0.009) but not Ix-2 (*p* = 0.073) vs. C • No group differences in non-technical skills (*p* = 0.285) After the Ix, but before the simulation: • **VAS-stress significantly lower in Ix-1** (*p* = 0.029) and Ix-2 (p = 0.035) vs. C, but no differences between Ix's (*p* = 0.897) • Thayer relaxation significantly lower in Ix-1 (*p* = 0.0.01) and Ix-2 (*p* = 0.0.035) vs. C, but no differences between Ix's (*p* = 0.709) • No differences in Thayer tension between Ix-1 (*p* = 0.275) and Ix-2 (*p* = 0.213) vs. C or between Ix's (*p* = 0.875)	0.90 (CLEAR) Good
C. High-Anxiety Populations			
High-Anxiety Populations: Stress/anxiety primary outcome			
* **Clark and Hirschman 1990** US, inpatient alcohol rehabilitation facility	STAI-state	• **STAI-state anxiety scores and self-reported tension significantly decreased** after each session for Ix and C (*p* < 0.0001 both metrics, groups) • **Ix had greater improvements than C in STAI-state** (*p* < 0.04) and tension (*p* < 0.0002) • **Ix had significantly lower STAI-state** scores than C following both sessions (*p* < 0.01 both)	0.50 (CLEAR) Poor
* **Chen et al. 2017** Taiwan, medical center	BAI	• Ix **significantly reduced BAI anxiety** between wks 0–4 (*p* = 0.001), 0-8 (*p* < 0.001), and 4–8 (*p* < 0.001); C did not (*p* > 0.05) • BAI was significantly lower for Ix than C at wk 8 (*p* = 0.033) • Ix but not C improved significantly from wks 0-8 in skin conductivity (*p* = 0.48), peripheral temperature (*p* = 0.007), HR (*p* < 0.0001), and breathing rate (*p* < 0.0001)	0.69 (CLEAR) Fair

Supplemental Table 4.2: Stress/anxiety metrics and outcomes of included studies (N = 58) by population and use of stress/anxiety as the primary or secondary outcome, Continued

Author, Year, Setting	**Stress/Anxiety Metric**	**Outcomes ****	**Quality Score, Tool** † (Boutron et al. 2005; NHLBI 2023)
* **Serafim et al. 2019** Brazil, hospital	HAM-A, BAI	After the Ix and at 10-wk follow-up: • **HAM-A and BAI were significantly lower ($p < 0.001$ for both)** • Depression and mania ratings were significantly lower ($p < 0.001$ and $p = 0.027$, respectively)	0.50 (NHBLI) Poor
High-Anxiety Populations: Stress/anxiety as secondary outcome			
* **Clark et al. 1985** UK, setting unclear	100-pt Likert scale, MMFQ	Compared w/before Ix: • Panic attack frequency significantly reduced during Ix ($p < 0.01$) and 2–13 wks after ($p < 0.05$) • **Anxiety levels significantly lower** ($p < 0.01$) during 15 min exposure to anxiety-provoking situation • **Anxiety/depression** ($p < 0.001$) and global distress ($p < 0.05$) significantly lower • No significant changes in BDI depression ($p > 0.05$)	0.73 (NHBLI) Fair
D. Clinical Populations (Acute)			
Clinical Populations (Acute): Stress/anxiety as primary outcome			
Biggs et al. 2003 US, private dental practice	DAR-S	• **No significant differences between any groups overall in dental-related anxiety** ($p = 0.67$), **post-Ix anxiety** ($p = 0.46$), **or anxiety reduction**, including C • C participants who used own anxiety reduction technique reported significantly less anxiety ($p = 0.04$)	0.38 (CLEAR) Poor
* **Hayama and Inoue 2012** Japan, hospital inpatient	Short-form POMS (Japanese version)	• Median post-chemo **POMS tension-anxiety significantly lower** among Ix vs. C ($p = 0.01$) • Both Ix and C showed significant reductions in pre-post chemo POMS tension-anxiety (both $p < 0.01$)	0.69 (CLEAR) Fair
* **Valenza et al. 2014** Spain, hospital	HADS-anxiety	• Following Ix, all variables were better and improved in Ix, w/**significantly improved HADS anxiety**, dyspnea, and mobility ($p < 0.001$ for all) ‡	0.63 (CLEAR) Fair
* **Bidgoli et al. 2016** Iran, hospital	SAI	Compared w/before Ix: • Ix but not C had **significantly reduced anxiety** at 30 and 60 min after Ix ($p = 0.0001$ both) • Anxiety decreases significantly greater in Ix than C ($p < 0.05$)	0.53 (CLEAR) Poor
Boaviagem et al. 2017 Brazil, maternity hospital	STAI (unclear whether state or trait)	• No differences Ix vs. C in mean **STAI** ($p = 0.58$ per-protocol, $p = 0.91$ ITT) • No differences in maternal pain/satisfaction or fatigue; delivery mode; Apgar scores ($p > 0.05$ all)	0.75 (CLEAR) Fair

Supplemental Table 4.2: Stress/anxiety metrics and outcomes of included studies (N = 58) by population and use of stress/anxiety as the primary or secondary outcome, Continued

Author, Year, Setting	Stress/Anxiety Metric	Outcomes **	Quality Score, Tool † (Boutron et al. 2005; NHLBI 2023)
* **Cicek and Basar 2017** Turkey, hospital delivery room	STAI-state	• Mean **STAI-state significantly lower** ($p < 0.001$) **in Ix vs. C for late active labor but not early or latent** ($p > 0.05$) • All labor phases (early latent, late latent, active) except transitional were shorter ($p < 0.05$) in Ix vs. C	0.69 (CLEAR) Fair
* **Chandrababu et al. 2019** India, hospital	STAI-state	From before surgery to 5th post-op day: • **STAI-state significantly reduced** in Ix ($p = 0.001$) but not C • This reduction was significantly greater in Ix than C ($p = 0.001$) • Ix had significantly less pain than C on 3rd post-op day ($p < 0.05$) • No between-group differences in pain on 4th or 5th days ($p > 0.05$)	0.73 (NHLBI) Fair
Ratcliff et al. 2019 US, university medical center	VAS-anxiety, STAI-state	Reduction in **VAS anxiety during biopsy** was: • Significantly greater in Ix-1 than Ix-2 ($p < 0.01$) and C ($p < 0.0001$) • Not significant differences between Ix-2 and C ($p = 0.65$) • Ix-1 had significant increase in beta current source density (CSD) in insula ($p = 0.006$) and ACC ($p = 0.019$) compared to C	0.64 (CLEAR) Fair
* **Grinberg et al. 2020** US, medical center	STAI-state	Compared to C, Ix group had significant: • **Lower post-procedural STAI-state ($p = 0.039$)** • Larger STAI-state decrease pre- to post-procedure ($p < 0.000$) • Lower HR post-procedure ($p = 0.048$) • Larger HR decrease pre- to post-procedure ($p = 0.01$) • No significant BP changes or differences ($p > 0.1$ all)	0.50 (NHLBI) Poor
* **Abo El Ata et al. 2021** Egypt, hospital	Burn-specific pain anxiety scale	Significantly **reduced burn-specific pain anxiety**: • Pre-to-post breathing exercises ($p = 0.000$) • Wk 1 (pre-Ix) to wks 2 and 3 (during Ix; $p = 0.000$) From pre- to post-breathing exercises, significantly reduced: • Pain ($p = 0.000$) • SBP ($p = 0.000$), DBP ($p = 0.000$), respiratory rate ($p = 0.000$), HR ($p = 0.000$) • From pre-post significantly increased relaxed behavior ($p < 0.002$)	0.64 (NHLBI) Fair

Supplemental Table 4.2: Stress/anxiety metrics and outcomes of included studies (N = 58) by population and use of stress/anxiety as the primary or secondary outcome, Continued

Author, Year, Setting	**Stress/Anxiety Metric**	**Outcomes ****	**Quality Score, Tool** † (Boutron et al. 2005; NHLBI 2023)
* **Hosseinzadeh-Karimkoshteh et al. 2021** Iran, medical center	Burn patient anxiety inventory	• On each of the 4 days, Ix had significantly **lower pain anxiety** than C ($p < 0.001$ all)	0.78 (CLEAR) Fair
* **Zahn and Kuonen 2021** Switzerland, university hospital	STAI, APAIS, VAS-stress	**Compared w/C, Ix intraoperative anxiety was**: • **Significantly lower for all measures** (STAI-state, $p = 0.0001$; APAIS, $p = 0.0003$; VAS, $p = 0.0007$) • **Significantly lower vs. pre-op for STAI-state** ($p = 0.007$) **and APAIS** ($p = 0.009$), but not VAS ($p = 0.79$)	0.64 (CLEAR) Fair
* **Moghadam et al. 2022** Iran, psychiatric hospital	BAI	Mean **anxiety was significantly lower** post-Ix: • Compared w/pre-Ix in both Ix's ($p < 0.001$) but not C ($p = 0.10$) • In both Ix groups vs. C ($p < 0.001$)	0.56 (CLEAR) Poor
* **Aktas and Ilgin 2023** Turkey, Ankara Hospital,	STAI	From pre-op to post-Ix: • **STAI-state significantly decreased in Ix-1** ($p = 0.007$) **but not Ix-2** or C • QoL significantly increased in Ix-2 ($p = 0.043$ both) and C ($p = 0.003$) but not Ix-1 • Post-Ix, significantly different in STAI-state across groups ($p < 0.05$)	0.37 (CLEAR) Poor
Clinical Populations (Acute): Stress/anxiety as secondary outcome			
* **Dhruva et al. 2012** US, university medical center	HADS-anxiety	• Ix was feasible (close to 100% compliance) • Sleep disturbance ($p = 0.04$) and **anxiety ($p = 0.04$) improved w/every h of** • **pranayama** practiced during Ix period From before-to-after 1st chemo cycle, no significant differences Ix vs. C in stress or other outcomes ($p > 0.05$ all)	0.63 (CLEAR) Fair
* **Park et al. 2013** South Korea, medical center	VAS-anxiety	Compared w/C and over the 3 days, Ix had significant: • Lower pain scores ($p = 0.01$) and reduction in pain scores ($p = 0.001$) • **Lower anxiety ($p = 0.01$) and reduction in anxiety ($p = 0.001$)** Ix had significantly reduced anxiety over the 3 days ($p = 0.02$)	0.67 (NHLBI) Fair

Supplemental Table 4.2: Stress/anxiety metrics and outcomes of included studies (N = 58) by population and use of stress/anxiety as the primary or secondary outcome, Continued

Author, Year, Setting	**Stress/Anxiety Metric**	**Outcomes ****	**Quality Score, Tool** † (Boutron et al. 2005; NHLBI 2023)
* **Eldin et al. 2015** Libya, hospital	STAI-state	Post-Ix, Ix but not C had significant: • **STAI decrease** all 3 days ($p = 0.003$ day 1, $p < 0.001$ days 2 and 3), and decrease was significantly greater than in C ($p < 0.001$) • Pain and pain behavior decreases ($p < 0.001$ both) • Improvement in respiration, HR, and BP ($p < 0.001$ all)	0.55 (NHLBI) Poor
* **Iyer et al. 2020** India, medical center	VAS-anxiety, PASS	Compared w/pre-Ix, **significant decreases** found after 1 and 7 days in ($p = 0.00$ all): • Pain • **Anxiety** • **Anticipatory anxiety**	0.73 (NHLBI) Fair
* **Ursavas and Catakli 2020** Turkey, hospital	HADS-anxiety	At 1,2,4,8,12, and 24 h post-op: • Pain: No significant between-group differences at any time point ($p > 0.05$ all) • **Compared to C, anxiety significantly lower in Ix ($p = 0.033$)** • Depression: No significant differences ($p = 0.081$)	0.68 (CLEAR) Fair
* **Lu et al. 2022** China, hospital	HADS	Compared w/C, Ix had significant differences in: • Dyspnea at T1 ($p = 0.037$), T3 ($p = 0.003$) • **HADS anxiety reductions** at T1 day before surgery ($p = 0.046$), T2, day after surgery ($p = 0.02$), T3 at discharge ($p < 0.001$) • Post-op complications ($p = 0.045$) • No between-group differences in 6 min walk test times at any time point ($p > 0.05$)	0.73 (CLEAR) Fair
E. Clinical Populations (Chronic)			
Clinical Populations (Chronic): Stress/anxiety as primary outcome			
* **Marshall et al. 2014** US, setting unclear	BAI	• **BAI was significantly lower after 4 wks** ($p = 0.0069$) • Among those w/o aphasia, COWAT-measured brain function, and verbal abilities significantly improved after 10 wks ($p = 0.0001$) • Among those w/aphasia, some speech-language measures significantly improved after 4 wks of guided practice ($p < 0.05$)	0.55 (NHLBI) Fair

Supplemental Table 4.2: Stress/anxiety metrics and outcomes of included studies (N = 58) by population and use of stress/anxiety as the primary or secondary outcome, Continued

Author, Year, Setting	Stress/Anxiety Metric	Outcomes **	Quality Score, Tool † (Boutron et al. 2005; NHLBI 2023)
Clinical Populations (Chronic): Stress/anxiety as secondary outcome			
* **Han et al. 1996** Belgium, setting unclear	STAI-state and trait	• From before to after Ix: HVS complaints significantly reduced (*p* < 0.001), based on Nijmegen Questionnaire • Inspiratory and expiratory time and tidal volume increased significantly (*p* < 0.001), but not end-tidal CO_2 (*p* > 0.05) • **State** (*p* < 0.001) **but not trait** (*p* > 0.05) **anxiety significantly reduced**	0.73 (NHLBI) Fair
* **Thomas et al. 2009** UK, primary care general practices	HADS-anxiety	At **6 mo following Ix**, **Ix had significantly greater improvements than C in** AQLQ (*p* = 0.01), **HADS anxiety** (*p* = 0.02), and depression (*p* = 0.03), and hyperventilation symptoms (p = 0.005) • No significant differences between groups in AQLQ, HADS anxiety or depression at 1 mo (*p* > 0.05 all) • Breathing training did not significantly change airway physiology, inflammation, or hyper-responsiveness (*p* > 0.05 all)	0.73 (CLEAR) Fair
Jefferson 2010 US, setting unclear	PSS, STAI	• SBP and DBP were decreased for Ix at 1-wk follow-up (*p* = 0.0001 and 0.02, respectively) but not 6 wks, and not for C (*p* > 0.05) • **No significant differences after Ix in PSS or STAI-state anxiety** for Ix or C (*p* > 0.05 all) • STAI-trait anxiety significantly decreased for Ix (*p* = 0.01) but not C (*p* = 0.09) at 1-wk post-Ix, but not at 6 wks (*p* > 0.05 both)	0.25 (CLEAR) Poor
* **Sureka et al. 2014** India, prison hospital	PGWBS-anxiety	**After 6 wks, Ix vs. C had significantly greater improvements in:** • Global functioning, depression, positive well-being, psychological general well-being, and general health (*p* < 0.01 for all) • **PGWBS-anxiety** (*p* < 0.01)	0.80 (CLEAR) Fair
* **Sureka et al. 2015** India, prison hospital	PGWBS-anxiety	**After 6 wks, Ix vs. C significantly improved in**: • GAF (*p* = 0.0002) • **Anxiety (*p* = 0.011)** • Positive Well-Being (*p* = 0.02) • General Health (*p* = 0.02) • Total PGWB (*p* = 0.05)	0.73 (CLEAR) Fair

Supplemental Table 4.2: Stress/anxiety metrics and outcomes of included studies (N = 58) by population and use of stress/anxiety as the primary or secondary outcome, Continued

Author, Year, Setting	Stress/Anxiety Metric	Outcomes **	Quality Score, Tool † (Boutron et al. 2005; NHLBI 2023)
Thomas et al. 2017 UK, general practices	HADS-anxiety	**12 mo after Ix:** • AQLQ significantly better in Ix-1 ($p < 0.001$) and Ix-2 ($p < 0.05$) vs. C • HADS-depression significantly lower in Ix-2 vs. C ($p = 0.03$) • No significant changes in lung function, asthma symptom control, or asthma exacerbation rate vs. C ($p > 0.05$ all) • **No significant differences in HADS-anxiety** pre-post Ix in all groups or between groups ($p > 0.05$ all)	0.80 (CLEAR) Fair
* **Fiskin and Sahin 2018** Turkey, medical center	DASS	**After 30 days, Ix had:** • PAI increase ($p = 0.000$), greater vs. C ($p = 0.000$) • **Stress/anxiety decrease** ($p = 0.000$), greater vs. C ($p = 0.000$) • Depression decrease ($p = 0.001$), greater vs. C ($p = 0.003$)	0.50 (CLEAR) Poor
* Watson et al. 2022 New Zealand hospital	5-point Likert Scale	**Compared w/Ix-2, Ix-1 significant initial increase** in: • QTc interval ($p < 0.0002$) • **Anxiety** ($p < 0.001$)	0.75 (CLEAR) Fair
F. Simulated Stress			
Simulated Stress Populations: Stress/anxiety as primary outcome			
Kamath et al. 2017 India, medical school	VAMS-anxiety	• **Ix showed trend** ($p > 0.05$) **toward lower VAMS anxiety** prior to, during, and following public speaking task	0.88 (CLEAR) Good
Simulated Stress Populations: Stress/anxiety as secondary outcome			
Holmes et al. 1978 US, university setting	Author-designed 18-item anxiety checklist	After threat or stimulation: • HR was significantly higher for threat vs. stimulation ($p < 0.001$), there were no significant differences between groups in stimulation condition, and it was significantly lower for C than Ix-1 or Ix-2 in threat condition ($p < 0.05$) • Skin resistance did not differ between groups or threat/stimulation conditions ($p > 0.1$) • **Significantly less anxiety reported in C vs. Ix-1 and Ix-2** ($p < 0.05$) • No significant differences in anxiety between Ix-1 and Ix-2 (p-value not reported)	0.33 (NHLBI) Poor

Supplemental Table 4.2: Stress/anxiety metrics and outcomes of included studies (N = 58) by population and use of stress/anxiety as the primary or secondary outcome, Continued

Author, Year, Setting	**Stress/Anxiety Metric**	**Outcomes ****	**Quality Score, Tool** † (Boutron et al. 2005; NHLBI 2023)
* **McCaul et al. 1979** US, university setting	Author-designed 18-item anxiety checklist	Following threat/stimulation: • **Ix-1 anxiety** significantly **lower** than in combined Ix-2 and Ix-3 ($p = 0.03$) • Self-reported ability to relax while awaiting shock significantly lower in expectation vs. no-expectation groups ($p = 0.02$) • Ix-1 vs. Ix-2 and Ix-3 combined had significantly lower skin resistance and pulse during threat anticipation ($p = 0.05$, $p = 0.02$, respectively) and threat ($p = 0.02$ both), but not HR (*p*-value not reported)	0.50 (CLEAR) Poor
Sakakibara and Hayano 1996 Japan, university setting	STAI-state	Following threat anticipation: • High frequency HRV during threat stayed the same for Ix-1 and significantly decreased (worsened) for Ix-2 and C ($p < 0.05$ for both); low-frequency HRV changes did not differ between groups (*p*-value not reported) • **STAI-state anxiety worsened in all groups**, w/no differences in changes between groups ($p > 0.05$)	0.50 (CLEAR) Poor
* Telles et al. 2019 India, residential yoga center	STAI-state	From pre- to post- each Ix: • Shape and size discrimination task errors significantly reduced after Ix-1 ($p < 0.001$) • **STAI significantly reduced after Ix-2** ($p < 0.05$) **and C** ($p < 0.001$) **but not Ix-1**	0.85 (CLEAR) Good
Meier et al. 2021 Canada, setting unclear	VAS-stress	**In response to Ix, no significant differences between groups for** cortisol ($p = 0.847$), alpha amylase (p = 0.735), or **stress** ($p = 0.986$) **In response to stressor:** • Ix-2 had significantly lower cortisol levels vs. C ($p = 0.045$), but no significant differences for Ix-1 vs. Ix-2 ($p = 0.052$) or C ($p = 0.955$) • **No significant differences between groups for** alpha amylase ($p = 0.38$) or **stress** ($p = 0.818$)	0.81 (CLEAR) Good
* **Sharma et al. 2022** India, university setting	STAI-state	**From pre- to post-Ix:** • Significant increase in attention task scores in Ix-4 ($p < 0.05$) • **STAI-state scores decreased significantly in Ix-1** ($p = 0.001$), **Ix-2** ($p = 0.008$), **Ix-3** ($p = 0.002$), **Ix-4** ($p = 0.042$) but not Ix-5 and Ix-6 ($p > 0.05$) • **Ix-1 had significantly lower STAI-state scores post-Ix vs. Ix-5** ($p < 0.05$)	100 (CLEAR) Good

Supplemental Table 4.2: Stress/anxiety metrics and outcomes of included studies (N = 58) by population and use of stress/anxiety as the primary or secondary outcome, Continued

Red font indicates an ineffective outcome for stress/anxiety. Bolded phrases in "Outcome" column reflect key stress/anxiety intervention outcomes. Bolded author names/years with asterisk (*) represent studies with at least one intervention that significantly reduced participants' stress/anxiety. APAIS, Amsterdam Preoperative Anxiety and Information Scale; AQLQ, Asthma Quality of Life Questionnaire; BAI, Beck Anxiety Inventory; betw, between; BDI, Beck Depression Inventory; BP, blood pressure; C, control; chemo, chemotherapy; COWAT, Controlled Oral Word Association Test; DAR-S, Dental Anxiety Scale Revised; dept, department; diff, difference; GAD-7, Generalized Anxiety Disorder-7; HADS, Hospital Anxiety and Depression Scale; HAM-A, Hamilton Anxiety Rating Scale; HF, high-frequency; h, hour; HR, heart rate; HVS, hyperventilation syndrome; IAMS, Immediate Anxiety Measurement Scale; ITT, intention-to-treat; Ix, intervention; LF, low-frequency; MMFQ, Marks and Matthews Fear Questionnaire; min, minutes; mo, month; PGWBS, Psychological General Well-Being Schedule; PHQ, Patient Health Questionnaire; PMR, progressive muscle relaxation; POMS, Profile of Mood States; PSS, perceived stress scale; pt, point; SAI, State Anxiety Inventory; signif, significant(ly); SAS-2, Sport Anxiety Scale–2; SDNN, standard deviation of the NN intervals; STAI, State-Trait Anxiety Inventory; STAI-C, State-Trait Anxiety Inventory for Children; VAMS, Visual Analog Mood Scale; VAS, Visual Analog Scale; vs., versus; w/, with; w/o, without; wks, weeks * $p > 0.05$ for impact of breath intervention on psychometric stress outcome. ** Primary outcomes listed first. † Quality scores for RCTs are from the CLEAR-NPT tool for non-pharmaceutical 2+ arm RCTs, with range definitions adopted from Chen 2012: <0.6, poor quality; 0.6–0.8 fair; >0.80 good. Those for non-RCTs are defined based on the National Heart, Lung, and Blood Institute (NHLBI) quality assessment tool's criteria, with the following author-determined range definitions to be consistent with those from RCTs: <0.6, poor quality; 0.6–0.8 fair; >0.80 good. ‡ The methods and results sections of this paper were found to be poorly written and difficult to interpret. Results reported here represent our best interpretation yet may misrepresent this study's findings. ‡‡ Textual descriptions of results in paper stated significance, table reported $p > 0.01$; thus p-value reported here is uncertain.

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CONCLUSION

The ability to fluidly coordinate our internal state with environmental dynamics fundamentally shapes our experience of and interaction with the world. This capacity derives from *(1)* the formation of temporal predictions to guide neurobehavioral state shifts and *(2)* flexibility that enables such shifts. When either of these processes goes awry, adaptive behavior gives way to more rigid responses, disrupting social interactions, communication, information transfer, and learning. This thesis thus examined temporal processing and allostasis in relation to dynamic attending.

Temporal Processing in Dynamic Attending

Due to the fleeting nature of our ever-changing environment, the most adaptive adjustments in state occur preemptively, guided by predictions based on prior experience. Such predictions are about not only *what* but also *when* an event will occur. Accordingly, Chapter 1 examined temporal processing and expectancy both in the brain and in behavior. Because behavioral measures of timing ability, such as sensorimotor synchronization (SMS), conflate motor skills and temporal perception, we sought a passive neural marker of temporal processing to disentangle the two. In this experiment, we assessed SMS via drum tapping and subsequently recorded electroencephalographic data during passive listening to a temporal auditory oddball paradigm. From the latter task, we compared the N1P2 auditory evoked potential to temporally expected beats to that elicited by deviant beats. This differential was found to predict SMS and, consequently, was proposed as a timing response index (TRI).

Allostasis in Dynamic Attending

Temporal expectancy cannot effectively guide internal state shifts without adequate state flexibility. Through a review and synthesis of the literature, Chapter 2 suggested that allostatic mechanisms mediate internal state shifts to enable state flexibility, thereby facilitating dynamic attention. While allostasis enables us to upregulate our arousal state to support adaptive responses to stressors, maintaining a chronic high-arousal allostatic state leads to pathology, a shift in baseline state, and state inflexibility. There, I also emphasized that diverse and cumulative stressors can induce chronic arousal. That is, arousal pathology can result both from chronic psychological stress and from chronic physiological stress due to poor sleep, low-quality diet, physical inactivity, and excessive technology use.

The experiment described in Chapter 3 provided evidence in favor of the arguments presented in Chapter 2, demonstrating an effect of health risk behaviors and poor emotional wellbeing on resting state oscillatory activity. Increased alpha and beta oscillatory power in individuals with greater allostatic load was interpreted as a stress-induced hypervigilant cortical state. This experiment, conducted on college students shortly after the end of the COVID-19 pandemic, only partially replicated experimental results of Chapter 1 and demonstrated different tapping patterns than before. A surprising dissociation between SMS and tapping regularity revealed a finer-grained relationship between these measures and the TRI. Since loneliness can impair synchronization ability (Saporta et al. 2023) and stress has been found to enhance neural responses to unexpected stimuli (Chang et al. 2015; Bangel et al. 2017; Zukerman et al. 2018; Ding et al. 2022; Ioakeimidis et al. 2023), these differences may reflect lingering effects of the pandemic.

Improving State Flexibility via Lifestyle Change

On the one hand, Chapters 2 and 3 underscored the detrimental impact of health risk behaviors on dynamic attending via allostatic load. On the other hand, these same chapters suggested that appropriate lifestyle modifications may reduce allostatic load and improve state flexibility. As a result, deficits in dynamic attending due to high allostatic load may be rectified with relatively simple behavioral changes, as outlined in the latter half of Chapter 2: improving sleep quality and diet, increasing physical activity levels, reducing psychological stress, and optimizing technology use can benefit the mind, brain, and body. Moreover, Chapter 4 illustrated the therapeutic potential of voluntary regulated breathing as an additional means of reducing psychological stress.

Future Directions

A resounding theme throughout this thesis is the profound interdependence of mental, physical, and brain states. Adaptive coordination with environmental demands entails alterations of all three, as perception and action are intricately intertwined. Despite this reality, the brain is often studied in a vacuum, divorced from its dynamic interaction with a multitude of peripheral signals. The framework proposed in this thesis, grounded in allostasis and dynamic attending, provides a lens through which we can perceive the cumulative effects of lifestyle and stress over time, which shape not only the body but also the brain. This systems perspective highlights the necessity of interdisciplinary collaborations between neuroscientists, physiologists, and psychologists to better understand the brain and body. Moreover, given the role of state flexibility in dynamic attention, allostatic load and self-regulatory factors should be examined in individuals with deficits in dynamic attending alongside more traditional tests of temporal processing. Lastly, recent trends in both mental and physical health should be understood in the context of modern developments and the COVID-19 pandemic. Increased prevalence of chronic disease, mental illness, and neurological disorders is likely attributable to high allostatic load due to health risk behaviors and, as a result, can be countered through changes in lifestyle. Public health initiatives and policies can help foster such behavior change and increase awareness of the widespread effects of physical activity, diet, psychological stress, sleep, and technology use on wellbeing. This thesis thus provides the groundwork not only for further research but also for application to improve individual health and society as a whole.

Knowledge is only power if we apply it.

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