STRESS AS A MEDIATOR OF OVEREATING AND THE EFFECTIVENESS OF MINDFULNESS TRAINING AS AN INTERVENTION STRATEGY

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".... and when the air hits my own brain, will I be the same?
I hope not, I hope to be better."

- Frank Vertosick Jr., MD

When the Air Hits Your Brain

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Abstract

Prolonged exposure to stress implicates the physiological system, which can have adverse effects on many health-related domains, including eating behavior. As the global prevalence of chronic stress continues to rise, it is imperative to investigate an intervention to reduce stress and its accompanying diseases. Stress-induced overeating, for example, can lead to the accumulation of visceral fat tissue, thereby increasing the risk of developing metabolic and cardiovascular diseases such as type 2 diabetes and hypertension. Stress-eating can, therefore, not only severely impact physiological health but can also greatly reduce an individual's quality of life. Mindfulness meditation, through its ability to regulate emotions and increase interoceptive awareness, could serve as a candidate to reduce stress as well as its subsequent maladaptive eating behavior. As the effects of stress and mindfulness can be observed on the behavioral and neuronal levels, the main aims of this dissertation project were threefold: 1) proof of concept: conduct a clinical trial to investigate the effectiveness of web-based mindfulness training and observe its corresponding neural correlates 2) identify the neural processing nodes fundamental for the sensory perception of food stimuli 3) conduct a clinical trial to investigate the effectiveness of a web-based, food-related, mindfulness training on stress-eating and observe its corresponding neural correlates.

The results of this dissertation project were able to demonstrate mindfulness training-induced reductions in stress and anxiety, as well as increases in perceived mindfulness, flow state, and attention. Additionally, the results were able to provide initial insight into the application of web-based mindfulness training as an intervention for stress-eating behavior through the observed reductions in perceived food cravings as well as stress- and emotional-eating tendencies. Furthermore, changes observed on the behavioral level were accompanied by changes on the neuronal level thereby emphasizing the effectiveness of mindfulness training as an intervention strategy. Moreover, through the completion of an extensive meta-analysis,

this dissertation was able to identify the neural processing nodes of the functional olfactory cortex, the results of which were utilized in subsequent neuroimaging analyses within the scope of this project.

In summary, this dissertation provides initial evidence of the effectiveness of web-based mindfulness training as an intervention strategy for stress as well as stress-eating behavior and should be considered for therapeutic or preventative treatment programs.

Abbreviations

ALE	Activation Likelihood Estimation
MA	Activation Probability Maps
ANOVA	Analysis of Variance
AG	Angular gyrus
ACC	Anterior Cingulate Cortex
AC-PC	Anterior Commissure - Posterior Commissure
ANIMA	Archive of Neuroimaging Meta-Analyses
ANT	Attention Network Test
BG	Basal Ganglia
BOLD	Blood Oxygen Level Dependent
BMI	Body Mass Index
BA31	Broadman Area 31
BMBF	Bundesministerium für Bildung und Forschung
CC	Cingulate Cortex
CSD	Constrained Spherical Deconvolution
COVID-19	Corona Virus Disease of 2019
DMN	Default Mode Network
DF	Degrees of Freedom
DTI	Diffusion Tensor Imaging
DWI	Diffusion Weighted Imaging
DLPFC	Dorsolateral Prefrontal Cortex
EPI	Echo Planar Imaging
TE	Echo Time
EEG	Electroencephalography
FOV	Field Of View
FLAIR	Fluid Attenuated Inversion Recovery
FCQ	Food Cravings Questionnaire
FCQ-S	Food Cravings Questionnaire - State
FCQ-T	Food Cravings Questionnaire - Trait
FA	Fractional Anisotropy
FD	Framewise Displacement
FWHM	Full Width Half Maximum
FC	Functional Connectivity
FMRI	Functional Magnetic Resonance Imaging
HT	Health Training
HRF	Hemodynamic Response Function
H+	Hydrogen
HPA	Hypothalamic-Pituitary-Adrenal
IPL	Inferior Parietal Lobe
INS	Insula
ISRCTN	International Standard Randomized Control Trial Number
T1	Longitudinal Relaxation Time
MRI	Magnetic Resonance Imaging
MPRAGE	Magnetization-Prepared Rapid Acquisition Gradient Echo
MTL	Medial Temporal Lobe
MCH	Melanin Concentrating Hormone
MAAS	Mindfulness Attention Awareness Scale
MBSR	Mindfulness Based Stress Reduction
MMT	Mindfulness Meditation Training
MNI	Montreal Neurological Institute
MB	Multiband
NMR	Nuclear Magnetic Resonance
OFC	Orbitofrontal Cortex
OSF	Open Science Framework
PSS	Perceived Stress Scale
POG	Postcentral Gyrus
PCC	Posterior Cingulate Cortex
PRESMA	Pre-Supplementary Motor Area
PFC	Prefrontal Cortex
PCASL	Pseudo-Continuous Arterial Spin Labeling
RF	Radio Frequency
RT	Reaction Time
TR	Repetition Time
RS-FMRI	Resting-State Functional Magnetic Resonance Imaging
RS	Restraint Scale
RUNC	Right Uncinate Fasciculus
SEES	Salzburg Emotion Eating Scale
SSES	Salzburg Stress Eating Scale
SARS-COV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SVC	Small Volume Corrected
T2*	Spin-Spin Relaxation Time
B0	Static Magnetic Field
SFG	Superior Frontal Gyrus
SLF	Superior Longitudinal Fasciculus
TP	Time Point
TP1	Time Point 1
TP2	Time Point 2
TMS	Transcranial Magnetic Stimulation
VPCC	Ventral Posterior Cingulate Cortex
VOI	Volume of Interest
VOXEL	Volumetric Pixel
H20	Water

1.0 Introduction

Stress [ˈstɹɛs] *(noun) can be defined as an organism's response to threatening stimuli in the environment.*

1.1 The Physiological Stress Response

The rapidly changing environment can contain threatening stimuli at any turn. The human body, however, through a series of physiological mechanisms, can produce an acute stress response that allows for the rapid and effective reaction to threatening stimuli in the environment. The acute stress response is regulated by subdivisions of the autonomic nervous system including the sympathetic and parasympathetic nervous systems as well as the hypothalamic-pituitary-adrenal (HPA) axis (McEwen, 2007; McEwen & Stellar, 1993). While the sympathetic nervous system elicits a series of immediate physiological changes, the HPA axis regulates the release of hormones necessary for initiating a stress response; together, the sympathetic nervous system and the HPA axis increase heart rate as well as the rate of respiration, elevates blood pressure, dilates pupils, tenses muscles, in addition to ensuring access to sufficient nutrients required to initiate a fight or flight response (Guilliams & Edwards, 2010; Joseph & Whirledge, 2017; Stephens & Wand, 2012). The parasympathetic nervous system, on the other hand, helps to restore the body to its initial state of homeostasis once the harmful stimulus has passed. These physiological systems are essential for survival, as they work together to ensure an effective response to threats in the environment.

Prolonged exposure to stress (i.e., chronic stress), however, can elicit persistent activation of the sympathetic nervous system, causing the aberrant production and release of stress hormones, thus ultimately dysregulating the HPA axis (McEwen, 2007; McEwen, 2008). Prolonged dysregulation of the HPA axis leads to abnormal physiological functioning and can contribute to the development of various physiological and psychiatric conditions. These include cardiovascular and immunological dysfunction, the accumulation of visceral fat tissue, osteoporosis, decreased neurogenesis, increased grey matter atrophy of the limbic system, as well as anxiety and depression disorders (Cohen et al., 2007; Conrad et al., 1999; Dich et al., 2015; Fineberg et al., 2013; Glover et al., 2006; Joëls et al., 2004; Kemeny, 2003; Kivimäki & Steptoe, 2018; McEwen, 2001; McEwen, 2008; Rosemberg et al., 2019; Sapolsky, 2003; Vanitallie, 2002; Weiss, 2007).

1.2 Stress & Eating Behavior

Not only has chronic stress been demonstrated to elicit a series of physiological and psychiatric diseases, but prolonged periods of stress can impact eating behavior. The dysregulation of the HPA axis can cause an excess of cortisol to be present in the bloodstream, which, in turn, can affect the hormone production of ghrelin, leptin, and neuropeptide Y. These hormones play an essential role in the body's perception of hunger and satiety (Bose et al., 2009; Holmes et al., 2010; Kuo et al., 2007; McEwen, 2007; McEwen & Stellar, 1993; Sojcher et al., 2012). Interestingly, the aberrant production of cortisol can additionally affect the storage of visceral fat tissue, as well as the body's metabolism (see Figure 1; adapted from Sojcher et al. (2012). Therefore, when the body is subjected to chronic stress, the resulting dysregulation of the HPA axis can affect eating behavior exhibited through increased feelings of hunger, increased caloric intake, as well as weight gain.

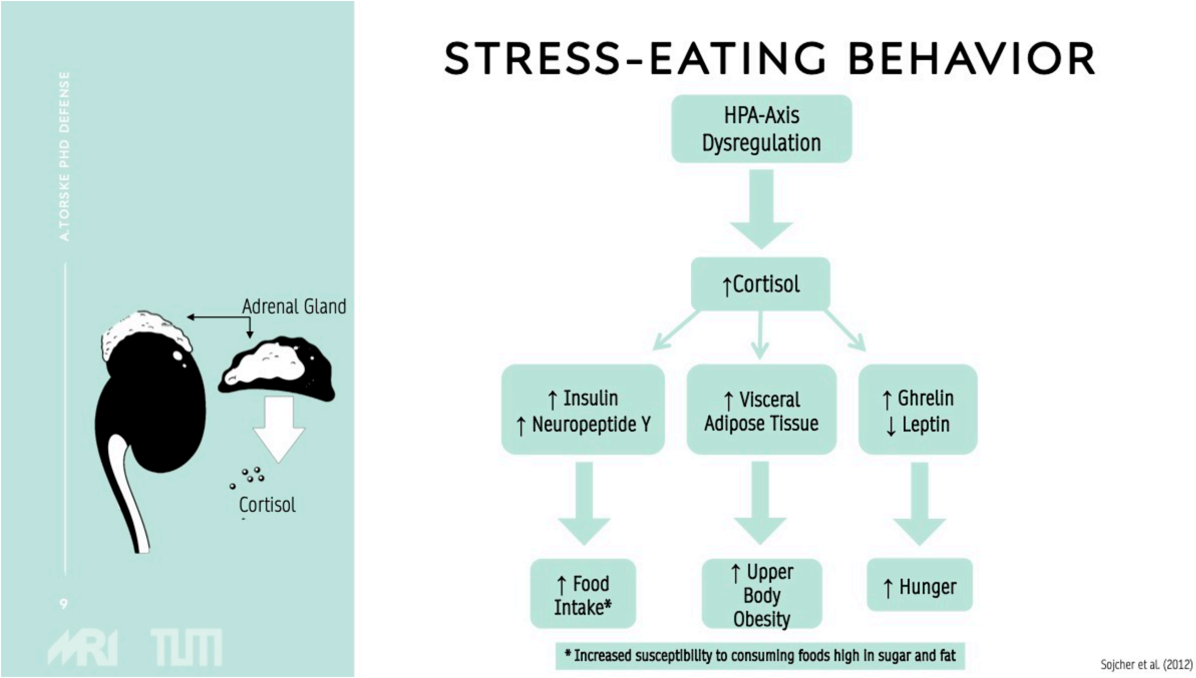

Figure 1: Depicts the cascading effects chronic stress has on the body's neuroendocrinological systems and its subsequent consequences on eating behavior. This figure was adapted from Sojcher et al. (2012).

Not only does the dysregulation of the body's physiological system affect appetite and eating behavior, but it can also have cascading effects on various psychological processes pertaining to executive functioning including the ability to regulate emotions (Mathews & MacLeod, 2005; Stansbury & Gunnar, 1994; Wang & Saudino, 2011). When stress hormones such as cortisol, adrenaline, and norepinephrine are released into the physiological system to prepare the body to engage in a fight or flight response, executive functions relevant to emotion regulation and cognitive control are implicated (Zimmermann & Stansbury, 2004). Stress can also have a significant effect on food-related decision-making abilities as well as on impulsive snacking and emotional eating behaviors (Mathews & MacLeod, 2005; Stansbury & Gunnar, 1994; Wang & Saudino, 2011). Moreover, individuals may seek relief or self-soothing mechanisms through high-calorie foods (Neseliler et al., 2017; Ulrich-Lai et al., 2015). This is due to the fact that the consumption of food high in sugar and fat releases neurotransmitters, such as dopamine, which are associated with pleasure and reward and can thereby help regulate the negative emotions elicited by stress (Parker et al., 2006; Tryon et al., 2013; Zellner et al., 2006).

The reduced ability to regulate emotions can lead to the formation of cognitive appraisals which, when faced with a stressor or negative emotion, may cause individuals to appraise the situation by seeking self-soothing mechanisms through food (Adam & Epel, 2007; Ozier et al., 2007; Ozier et al., 2008). The recurrent association of engaging with foods high in sugar and fat, which seemingly alleviates the psychological consequences of stress, promotes the repeated engagement in this behavior which can also be referred to as reinforcement learning or the learned association between stimuli. Reinforcement learning can ultimately lead to habit formation, which, within the context of stress eating, perpetuates the consumption of high-calorie foods (Klatzkin et al., 2019; Schaefer et al., 2021). While the association between stress, the physiological stress response, and the development of emotional eating patterns is clear, the problematic nature of this relationship becomes even more evident when considering the high societal prevalence of chronic stress in addition to the obesogenic environments (which are defined as living conditions with persistent exposure to high-calorie food items) in which much of the global population resides.

Therefore, not only are stressed individuals more susceptible to experiencing an increase in appetite due to the aforementioned dysregulation of the HPA axis, but the inability to effectively exert cognitive control or restraint within these obesogenic environments renders individuals even more susceptible to engaging in stress-related overeating behavior (Hawkes, 2006; Lake & Townshend, 2006; Swinburn et al., 2011). While previous research has repeatedly demonstrated the impact chronic stress has on the physiological and cognitive systems including eating behavior, body metabolism, as well as executive functioning, little is known about the mechanisms through which stress-eating behaviors can be intervened and therefore requires further research.

1.3 Olfaction, Food, and the Sensory System

Not only should the scientific community foster research on stress-reduction mechanisms, but it would additionally be advantageous to investigate the biological mechanism of olfaction, which is fundamental in the processing of food stimuli to further explore eating behavior. Olfaction, or the sense of smell, is one of the oldest evolutionary senses that has enabled organisms to extract valuable information from the environment. Odorous information is rapidly processed by the cerebral system to initiate behavioral responses ranging from finding food and mates, and avoiding predators or threats (Boesveldt et al., 2010; Hoover, 2010; Sorokowska et al., 2017). In fact, our sense of smell is linked with the physiological stress response such that negative (i.e., potentially dangerous or harmful) odors are prioritized by the cerebral system to allow for the rapid initiation of a fight or flight response (Boesveldt et al., 2010; Iravani et al., 2021). Not only is the sense of smell linked to stress or the detection of threatening stimuli, but it also has a significant influence on eating behavior. Previous research was able to demonstrate that the mere detection of food odors can elicit a series of biochemical and physiological responses. These responses include the release of saliva and digestive enzymes that prepare the body for the ingestion and digestion of food, while simultaneously eliciting appetite-enhancing effects, thereby motivating the organism to seek food (Ramaekers et al., 2016; Smeets et al., 2010). The rapid, physiological, response to the presence of food odors is an essential evolutionary mechanism to motivate organisms to eat, especially in times of food scarcity (Hoover, 2010). However, despite the evolutionary adaptations of the olfactory system to help organisms maintain sufficient nutrient levels, the stressful and obesogenic conditions of the modern world lead individuals to succumb to stress-related overeating behavior.

1.4 Stress, Malnutrition & Health

Given the profound effect chronic stress has on the physiological, cognitive, and psychological systems, individuals who are frequently exposed to stressful situations and – consequently – engage in stress-eating behaviors, could be susceptible to long-term health consequences. For example, frequently engaging in stress-eating behaviors can increase caloric intake which can lead to significant weight gain. Given the prominent role chronic stress has taken in modern society, the prevalence of individuals engaging in stress-eating and snacking behavior continues to rise. In fact, the onset of the SARS-CoV-2 pandemic and its lockdown measures not only had an impact on emotional well-being exhibited through increased stress, anxiety, and depression levels, but also had a significant impact on eating behavior (Burnatowska et al., 2022; Madalı et al., 2021; Shen et al., 2020). Moreover, the COVID-19 pandemic cast a spotlight on an increasing central health issue namely chronic stress and its long-term health consequences. Not only does stress-induced overeating behavior lead to the accumulation of visceral fat tissue, but it can also have negative implications on metabolic and cardiovascular health. For example, stress-related overeating and its subsequent weight gain have been demonstrated to contribute to the development of conditions such as type 2 diabetes, hypertension, and cardiovascular disease, all of which can severely impact both physical health as well as quality of life (Bray, 2004; Epel et al., 2000; Gami et al., 2007; Torres & Nowson, 2007).

In addition, studies observing the trends in body mass index (BMI), a numerical value utilized within the medical community to provide an estimate of body composition based on weight and height, have demonstrated that an elevated BMI is associated with an increased risk of developing cardiovascular and metabolic diseases (Sturm, 2007). In fact, in recent years, a BMI of over 40 (which indicates the classification of severe obesity) has increased by 50% and the occurrence of a BMI exceeding 50 has increased by 75% (Sturm, 2007). It is therefore apparent, that the prevalence of maladaptive overeating behavior continues to rise. Given the negative implications chronic stress has on the body (Benjamin et al., 2019; Hales et al., 2020; Virani et al., 2020), it is imperative that the scientific community contribute to the investigation of intervention mechanisms for stress-related malnutrition.

2.0 Contemplative Science & Mindfulness Meditation

Contemplative science is an interdisciplinary field of research investigating the effects and mechanisms of contemplative practices such as yoga and mindfulness meditation. These practices are founded upon the principle that the mind and body (i.e., emotional states and physical health) are bidirectionally connected. For example, in recent years, mindfulness meditation training (MMT) which involves the intentional focus of attention of the present moment without judgment or distraction (Kabat-Zinn, 2003a), has been extensively studied. This research demonstrated MMT to effectively reduce stress as well as improve overall well-being (Creswell & Lindsay, 2014; M. Goyal et al., 2014a; Hariprasad et al., 2013; Hölzel et al., 2011; Luders et al., 2013; Pickut et al., 2013; Sharma & Rush, 2014). Through the ability to cultivate the awareness of thoughts, emotions, and bodily sensations, MMT facilitates the development of greater interoceptive awareness, emotion regulation, in addition to the reduction of stress sensitivity (Butzer et al., 2015; Chong et al., 2011; D'Silva et al., 2012; Gard et al., 2014; M. Goyal et al., 2014b; Lemay et al., 2019; Wahbeh et al., 2008). This heightened awareness allows individuals to observe stressors with greater objectivity and compassion, leading to the reduction of both the physiological stress response as well as the susceptibility to chronic stress (Creswell & Lindsay, 2014; Marcus et al., 2003; Miller et al., 2021). Given its effect on stress, MMT should be considered as a possible intervention strategy for individuals who suffer from stress-related overeating behavior.

2.1 Mindfulness Meditation & Stress Eating

Conventional dieting methods enforcing calorie restriction and the elimination of certain macronutrients have become widely known for their claims to be effective weight loss mechanisms. These diet methods and their strict regiments, however, leave little room for individuals to follow natural hunger and satiety cues. This can, in turn, increase the risk of developing maladaptive eating behaviors. MMT, in comparison, can not only enable increased awareness of stress cues in the environment but can also enhance the awareness of bodily sensations. MMT can therefore increase stress sensitivity as well as increase the awareness of natural hunger and satiety cues. Greater awareness of hunger cues can help prevent individuals from engaging in mindless snacking or emotional eating tendencies, even when no hunger is perceived.

To this end, researchers have taken initial steps in investigating the effects of MMT on maladaptive eating behaviors such as binge-eating disorder (Katterman et al., 2014; Kristeller & Hallett, 1999) as well as investigating its effects on individuals with obesity (Daubenmier et al., 2011; Sampaio et al., 2021). While these findings have been able to demonstrate improvements in eating behavior in clinical populations, further research is required to understand the underlying effect MMT has on eating behavior. The aim of this dissertation project is therefore to determine MMT's effects on reducing stress-related overeating behavior.

3.0 Neuroimaging

To gain valuable insight into the association between human behavior and its underlying neural mechanisms, neuroimaging is a non-invasive technique frequently utilized within the field of neuroscience to explore this relationship. Through its ability to observe brain structure, function, and connectivity, neuroimaging methods allow for the investigation of the neural mechanisms underlying various cognitive processes, emotions, behaviors, and disorders. Therefore, to acquire a deeper understanding of the neural mechanisms underlying the relationship between stress, eating behavior, and MMT, magnetic resonance imaging (MRI) was utilized within the scope of this dissertation project.

3.1 Magnetic Resonance Imaging | MRI

To obtain in-vivo structural and time series images of the brain, MRI utilizes the phenomenon of nuclear magnetic resonance (NMR) which is founded upon the properties of atomic nuclei and how their spin (i.e., precession) changes when subjected to a magnetic field and/or radiofrequency (RF) pulses. Due to the high water (H_20) content of human tissue, fats, proteins, and carbohydrates, hydrogen protons (H+) serve as a source nucleus for the MRI technique.

When H+ atoms are exposed to a strong magnetic field (B0), H+ align parallel or antiparallel to the magnetic field. Once the protons are aligned, an RF pulse can be applied at the resonant frequency of the H+, thus exiting the proton spin and transferring the protons located within the RF pulse into a higher energy state. Once the RF is switched off, the protons transmit weak RF signals varying in strength during their return to equilibrium. Receiver coils within the

MRI machine can detect the signals and convert them into electrical signals to capture the change in energy state. The rate at which the hydrogen nuclei return to equilibrium is referred to as relaxation time and serves as the basis of the MRI image. Modern MRI machines incorporate gradient magnetic fields to produce multiple variations in the magnetic field strength across the imaging volume. This ultimately allows the image to contain spatial information. The digitized, electrical, signals, captured by the receiver coils are Fourier transformed, which converts the signal from the time domain to the frequency domain, thereby also allowing for the separation of the signal into different frequency components. At this stage, the data is represented in k-space, which effectively contains information pertaining to spatial frequencies as well as phase information of the encoded signal. Advanced mathematical algorithms, including Fourier reconstruction techniques, are utilized to convert k-space into two- or three-dimensional MRI images. Given that different tissue types (e.g., tissue, bone, blood) all have differing magnetic properties, the MRI signals differ, thereby allowing for the differentiation (or contrast) of the various tissue types within the image. In an MRI image, the image is divided into three-dimensional units called voxels (i.e., volumetric pixels). Each voxel represents a small volume element and contains information pertaining to the signal strength within said voxel. Differences in signal strength or intensity help to determine different tissue types in the brain (or imaged organ). The three-dimensional image, which consists of signals from multiple voxels, can now be utilized to derive information about the structure and tissue differentiation (e.g., grey matter, white matter, and cerebral spinal fluid) of the brain.

3.1.1 Functional Magnetic Resonance Imaging

Functional magnetic resonance imaging (fMRI) is a neuroimaging technique within which multiple MRI measurements are acquired in rapid succession to measure changes in brain activity over time. To capture brain activity, fMRI relies on changes in blood flow (and the corresponding change in oxygen levels) to provide insight into brain activity during a given task. This imaging technique is founded upon the blood-oxygen-level-dependent (BOLD) effect. The BOLD effect presupposes that when a particular brain region is active, blood flows to that area of the brain thereby providing it with an increased supply of nutrients (e.g., oxygen). An increase in oxygen concentration alters the magnetic field in that region, causing local field distortions initiated by the displacement of deoxygenated blood with oxygenated blood. It is through these local field distortions generated by the displacement of deoxygenated blood that is critical for the generation of BOLD images utilized in fMRI. However, it is important to note that BOLD imaging is an indirect measurement of brain activity, in which there is an assumption that an increase in the concentration of oxygenated blood indicates increased neural activity. Nevertheless, researchers have investigated the biological basis of the BOLD signal and have gained a foundational understanding pertaining to the complex interplay between the local blood flow, blood volume, as well as the metabolic rate of oxygen to support BOLD imaging as an indirect measure of brain activity (Logothetis & Wandell, 2004). The fMRI technique, therefore, plays a unique role within the field of cognitive neuroscience as it allows study aparticipants to be presented with various stimuli within the MRI scanner, thereby providing the scientific community with essential insights into the functional mechanisms underlying various cognitive processes and emotional states.

Given that the fMRI technique can capture important information regarding the rapid delivery of blood to the active neuronal tissue, this technique allows for the detection of active brain areas during a stimulus presentation. To accurately derive information from the BOLD signal, the hemodynamic response function (HRF) must be taken into account. The HRF accounts for the fact that the delivery of the oxygenated blood in the active neuronal area is not instantaneous; the HRF is, therefore, modeled onto the fMRI images to account for the delay in hemodynamic response, thus allowing for a more accurate interpretation of fMRI data and the neuronal response to a given stimulus.

3.1.2 Resting-State fMRI

Not only can MRI images capture the neuronal response to a particular stimulus or experimental condition, but resting state fMRI (rs-fMRI) is another neuroimaging technique utilized to capture intrinsic brain activity. While rs-fMRI acquisition does not subject the participant to a particular stimulus, this neuroimaging method enables researchers to investigate underlying neuronal activity at rest. In addition to capturing intrinsic brain activity, rs-fMRI can provide valuable information regarding the synchronization of spontaneous neural activity between different brain regions at rest. This is known as rs-fMRI functional connectivity (FC). This measure can serve as a marker for the degree to which various brain areas communicate with one another in the absence of a task or stimulus. For example, while an increase in FC between brain regions can imply stronger coupling (i.e., the degree to which the neural activity of one region is related to the neural activity of another region), a decrease in functional connectivity can imply a decoupling of the dependence between brain areas. Observed alterations in FC can, therefore, provide insight into various neural processes and how these processes relate to other brain areas.

3.1.3 Diffusion Tensor Imaging

While BOLD imaging can provide information on the brain’s synchronous activity through FC metrics, diffusion tensor imaging (DTI) differentiates itself from BOLD imaging as it provides insight into the microstructural organization of the brain’s white matter, thereby shedding light on the structural connections as well as the integrity of tracts between brain areas. The brain's white matter consists of axons that serve as communication highways between different brain areas. The DTI method allows for the observation of the movement (direction and magnitude) of water molecules within white matter tracts. Not only does DTI provide information on the underlying organization of the brain's microarchitecture, but changes in brain organization can be observed when conducting a longitudinal, intervention study. MRI can therefore not only provide valuable insight into the underlying functional organization of the brain but can also provide information on the brain's structural organization.

3.1.4 Meta-analyses

As the neuroimaging field and its accompanying MRI research continue to grow, the number of annual studies in peer-reviewed journals also increased. In an effort to provide the scientific community with an overview of all available literature on a given topic, researchers utilize meta-analyses, a statistical technique to quantify and analyze data from multiple, independent, studies to obtain an overall estimate of the effect of interest. With regard to fMRI neuroimaging studies, the activation likelihood estimation (ALE) method is utilized to quantify all relevant and available data which allows for a formal statistical analysis to be conducted to obtain interstudy concordance (Eickhoff et al., 2009; Turkeltaub et al., 2002). ALE's allow for the pooling of MRI coordinates of significant brain activations and can calculate the probability of activation at each voxel of the brain across studies. ALE's can therefore identify the most consistent and reliable areas of brain activation across studies, thereby providing the scientific community with a robust overview of the neuroimaging literature on a particular topic under investigation.

3.2 Eating Behavior, Stress, MMT, and the Brain

Neuroimaging research can be applied to a multitude of research questions including the investigation of stress, eating behavior, as well as MMT and its underlying neuronal mechanisms. For example, not only has MMT been attributed to the ability to increase emotion regulation, interoceptive awareness, as well as the reduction of stress sensitivity on the behavioral level (Butzer et al., 2015; Hölzel et al., 2011; Lemay et al., 2019; Wahbeh et al., 2008), but extensive neuroimaging research on MMT practitioners has observed differences in brain structure and function in areas previously attributed to having an influence on executive functioning including emotion regulation as well as interoceptive awareness.

For example, the amygdala, hypothalamus, and insula are brain areas that have been implicated in exhibiting neuroplastic changes in MMT practitioners; this is an important finding as these brain areas play a unique role in emotion processing, interoceptive awareness, as well as regulating the stress response (Cacciaglia et al., 2017; Hariprasad et al., 2013; Hölzel et al., 2011; Luders et al., 2013; Pickut et al., 2013; Roozendaal et al., 2009; Sapolsky, 1996; Zavorotnyy et al., 2018). For example, the hypothalamus is considered to be a brain area that plays a central role in the regulation of stress and has been demonstrated to play a role in eating behavior when considering the impact chronic stress has on inducing aberrant HPA axis functioning (Bose et al., 2009; Holmes et al., 2010; Kuo et al., 2007; McEwen & Stellar, 1993; Sojcher et al., 2012). In fact, to further investigate its effects on eating behavior, the hypothalamus can be separated into two nuclei to investigate its unique effects on eating behavior: namely the medial and lateral hypothalamus.

While the medial hypothalamus, through its ability to regulate the release of hormones such as melanin-concentrating-hormone (MCH), has been demonstrated to play a role in regulating perceived satiety (Saper et al., 2002), the lateral hypothalamus, on the other hand, has been implicated in the perception of hunger through its regulation of hormones that stimulate eating behavior such as neuropeptide Y and agouti-regulated peptides (Aston-Jones et al., 2009; Bernardis & Bellinger, 1996; Saper et al., 2002; Syan et al., 2021). Interestingly, a recent review that sought to investigate differences in intrinsic FC patterns between individuals with obesity in comparison to controls was able to demonstrate FC differences between the medial hypothalamus, a brain area that plays a role in regulating satiety cues, and areas of the reward system (Syan et al., 2021). This observation suggests that individuals with obesity may have an increased interdependence between perceived reward and satiety. An additional finding in the review revealed that individuals with obesity demonstrated greater FC between somatosensory areas and the lateral hypothalamus, which is an area of the brain that plays a role in regulating hunger cues. These results not only indicate that individuals with obesity may have increased sensitivity to both sensory aspects of food as well as the perception of hunger when compared with controls, but the results additionally provide evidence that differences in eating behavior are accompanied by changes on the neuronal level.

Given MMT's ability to impact stress sensitivity and emotion regulation, MMT may also, through the HPA axis, affect hypothalamic structure and function, thereby ultimately affecting eating behavior. The hypothalamus and its involvement in the complex interplay between stress, appetite, and eating behavior may provide valuable insight into the neuroplastic changes elicited by MMT.

While the hypothalamus has been demonstrated to play a prominent role in stress and eating behavior, another brain area of interest, namely the insula, is also involved in regulating eating behavior. For example, the insula has been implicated in the perception of bodily sensations, as well as in attentional control (Craig, 2009). Notably, these two aspects are fundamental in both MMT and eating behavior. More specifically, the literature provides extensive evidence pertaining to the insula's role in the subjective processing of odor, flavor, and texture, which are integral factors in the assessment of the edibility and reward of food (Rolls & McCabe, 2007; Small, 2010; Torske et al., 2022). Similar to the hypothalamus, the insula can be divided into individual processing nodes (namely the anterior and posterior insula) to allow for a closer examination of its distinct roles in mindfulness, stress, and eating behavior.

The anterior insula, for example, has been associated with emotion regulation as well as interoceptive awareness in the context of MMT practitioners (Farb et al., 2012; Hölzel et al., 2007; Laneri et al., 2017). Emotion regulation and interoceptive awareness are particularly relevant to eating behavior as these qualities enable individuals to become more aware of hunger and fullness cues, thereby facilitating more mindful food choices that are less driven by emotions (Craig, 2009; Critchley et al., 2004). In addition, the posterior insula has been implicated in sensory processing as well as the integration of taste and smell (Rolls, 2006). Interestingly, both the anterior and posterior insula have been found to integrate signals from hormones pertaining to eating behavior such as ghrelin and leptin (Wright et al., 2016). Therefore, while the anterior insula has been attributed to the regulation of emotions and interoceptive awareness, the posterior insula can be attributed to the sensory integration of food-related stimuli. The insula, therefore, not only plays a fundamental role in facilitating interoceptive awareness as well as cognitive and emotion regulation but also plays a fundamental role in sensory processing fundamental in influencing food choice.

While several brain areas have been implicated in both stress and MMT, initial research on the FC of brain areas associated with MMT has been conducted and could successfully demonstrate MMT-induced FC changes (Bremer et al., 2022; Creswell et al., 2016; Sezer et al., 2022; Taren et al., 2015; Taren et al., 2017). However, it is important to note that previous studies investigating MMT-induced FC changes implemented general MMT interventions. The aim of this dissertation project was, therefore, to investigate MMT's influence on eating behavior through the application of a food-specific MMT, in addition to gaining further insight into the complex interplay between stress, appetite, and eating behavior on both the behavioral and neuronal levels.

4.0 Main Aims & Scope:

This dissertation project aims to examine the influence of stress on eating behavior and its underlying neural correlates. What makes this project unique, is the investigation of a food-specific MMT as an intervention strategy for stress-related overeating while observing its effects on both the behavioral and neuronal levels. The results of this dissertation project could provide critical evidence for an intervention that can be utilized to improve overall well-being in addition to cultivating a more mindful relationship with food. If MMT serves to be an effective intervention strategy for stress-related overeating behavior, the long-term benefits of a food-related MMT could ultimately help individuals reduce the risk of developing cardiovascular and metabolic diseases.

4.1 Project 1: Validation of Web-Based MMT:

The Effects of Web-Based Mindfulness Training on Psychological Outcomes, Attention, and Neuroplasticity

The aim of Project 1 was to investigate the effectiveness of a web-based MMT on various psychological outcomes including stress, anxiety, attention, physical well-being, and flow, in addition to assessing its corresponding neuroplastic changes. While initial research on web-based MMT demonstrates improved self-compassion, perceived stress, cognition, mindfulness, and reduced anxiety and depression symptoms (Glück & Maercker, 2011; Krusche et al., 2013; Sevilla-Llewellyn-Jones et al., 2018; Yogeswaran & El Morr, 2021), it is imperative to continue to elucidate whether a web-based MMT course can also reliably improve mental health and physical well-being in comparison to in-person MMT. If successful, web-based MMT could provide a larger portion of the population, who may not have access to in-person MMT (whether it be for logistical or financial reasons) with the necessary tools to improve their overall mental health and physical well-being. In addition, if web-based MMT is demonstrated to be as effective as in-person MMT, it could be utilized as a tool for more specific (i.e., targeted) health-related topics (e.g., stress-eating behavior).

4.2 Project 2: Localizing the Human Brain Response to Olfactory and Food Stimulation

Given that the overall aim of this dissertation project is to explore the effects of MMT on eating behavior, key regions of interest essential in the processing of olfactory stimulation, which is an essential mechanism underlying the hedonic processing of food, should be considered. However, over 1,000 new neuroimaging studies exploring the functional neuroanatomy of the olfactory cortex have been published since 2013 alone. Therefore, to identify the most consistent and reliable areas of brain activation during the presentation of food stimulation across studies, the aim of Project 2 was to conduct a robust overview of the neuroimaging literature involving the functional neuroimaging of olfactory processing. To this end, an ALE was conducted to gain insight into the functional neuroanatomy of olfactory stimulation and its processing nodes. The results of the ALE provide important information on the brain areas of interest when observing the neuronal effects of MMT on eating behavior.

4.3 Project 3: Mind*ful*ness Training Reduces Mind*less* Eating Behavior:

The effects of a food-related mindfulness training on stress-eating and brain function.

As both stress and mindfulness have an effect on the neuronal level, the aim of Project 3 was to investigate the effects of a food-related MMT on the behavioral as well as neuronal levels. To this end, participants completed self-report measures and underwent rs-fMRI. The results of this study provide insight into the neural processes underlying the mechanisms through which MMT influences stress-eating behavior, while also supporting MMT as a possible intervention mechanism for stress-eating behaviors in addition to other clinical populations.

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Effects of web-based mindfulness training on psychological outcomes, attention, and neuroplasticity

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Mindfulness meditation training (MMT) reliably reduces stress and anxiety while also improving attention. The primary aim of this study was to investigate the relationship between MMT, stress and anxiety reduction, and its impact upon improvements in attention on the behavioral and neuronal levels. As a second aim, we sought to explore any relationship between MMT, attention, and modified states of mind such as flow. 118 healthy, meditation-naïve, participants were either assigned to a 31-day, web-based, MMT or an active control, health training (HT). Participants underwent functional magnetic resonance imaging while performing the attention network test (ANT) to assess functional and behavioural attentional changes, diffusion tensor imaging (DTI) to assess microstructural neuronal changes and completed relevant questionnaires to explore changes in psychological outcomes. Results confirmed a reduction in perceived stress and anxiety levels in the MMT group and significant improvements in the overall reaction time during the ANT, albeit no specific effects on the attentional components were observed. No statistically significant changes were found in the HT group. Interestingly, a significant group-by-time interaction was seen in flow experience. Functional data exhibited an increased activity in the superior frontal gyrus, posterior cingulate cortex, and right hippocampus during the alerting condition of the ANT after the MMT; decreased stress and trait anxiety were significantly correlated with the activation in the right hippocampus, and increased flow was also significantly correlated with all the aforementioned areas. DTI data showed increased fractional anisotropy values in the right uncinate fasciculus indicating white matter microarchitecture improvement between the right hippocampus and frontal areas of the brain. This study, therefore, demonstrates the effectiveness of web-based MMT on overall well-being and attentional performance, while also providing insight into the relationship between psychological outcomes, attention, and neuroplastic changes.

Mindfulness meditation is defined as present-centered awareness of thoughts, feelings, or sensations acknowledged and accepted free of judgment[1]. In this paper, we used the term mindfulness meditation training (MMT) to refer to any program or training that incorporates mindfulness meditation in their practice. MMT has been demonstrated to notably improve perceived stress[2–5], anxiety, and consequently mental health[2,6–9], while also playing a role in improving various domains of cognitive function including attention, working memory, and problem-solving skills[10–13]. On the other hand, prolonged periods of stress and anxiety can elicit a wide range of physical and psychiatric diseases[14], showing detrimental effects on cognitive performance[15–19]. One of the main cognitive processes affected by chronic stress and anxiety is attention[18,20]. Attention is generally defined as an

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essential domain of cognitive functioning that allows for the selection of stimuli for further processing[21]. While acute stress, from an evolutionary standpoint, plays a crucial role in drawing attention to threatening stimuli, chronic or disordered stress can have a negative effect on the ability to distribute attentional resources efficiently, thereby implicating cognitive functioning[22]. An additional adaptive response to threats in the environment is anxiety. Like stress, anxiety can become maladaptive in trait anxious individuals causing deficits in cognitive functioning through the similar, inefficient, distribution of attentional resources[18]. While stress and anxiety have been demonstrated to have a negative impact on cognitive, or attentional, functioning as a whole[15–18], a recent meta-analysis conducted on MMT was able to demonstrate that MMT can, overall, have a positive influence on attentional mechanisms[23]. Given the documented detrimental effects of stress and anxiety on cognitive function and the positive effects of MMT on attention, we investigated whether stress and anxiety reduction following mindfulness training would be related to improvements in attention both on the behavioral and neuronal level.

To examine the effects of MMT on the different components of attention, this work followed Michael Posner's attention network model which encompasses three attentional mechanisms that rely on specific, separate, networks in the brain: Alerting (i.e., vigilance), orienting (i.e., selection), and executive control (i.e., the process of blocking distractors while performing a task)[24–27]. These attentional mechanisms can each be measured via the attention network test (ANT)[28]. Posner's ANT was therefore utilized in the present study to investigate: a) the effects of a web-based MMT on the different attentional components and psychological outcomes, b) any link between psychological outcomes and improved attention, and c) brain functional and anatomical changes.

Not only was previous research able to determine MMT's effects on attentional mechanisms, but it was also demonstrated to have a positive effect on the psychological flow experience[29]. The concept of flow was introduced by the Hungarian psychologist, Mihaly Csikszentmihalyi, where he defined flow as a state of consciousness of optimal concentration and absorption in a given task which leads to a state of satisfaction or optimal experience[30]. Though research on flow is nascent, a recent study showed that an increase in flow experience has a positive impact on the ability to sustain attention[31]. Given the positive effect of MMT on flow and the close relationship between flow and attention, we thought that it would be interesting to investigate the association between MMT, flow-experience, and attention, in addition to how the reduction of stress and anxiety could lead to improvements in attention. To elucidate these associations, we used magnetic resonance (MR) neuroimaging techniques, in addition to standardized questionnaires, to determine the mechanisms underlying these relationships and changes.

To date, neuroimaging studies have implicated several brain areas as playing a role in attentional processing such as the cingulate cortex (CC), prefrontal cortex (PFC), and hippocampus[32–34]. Interestingly, the CC, PFC, and hippocampus have also been demonstrated to exhibit MMT elicited neuroplastic changes[35–37]. For example, while previous functional magnetic resonance imaging (fMRI) studies have attributed the anterior cingulate cortex (ACC) to the processing of executive control[38], several studies were also able to attribute greater ACC activation in experienced meditators[39,40] in addition to observing an increase in ACC activation as a direct result of MMT[35]. Interestingly, improvements in executive control have also been observed following short MMT interventions, which comprised of 20-min practice sessions per day for 3 to 5 days[41,42]. In fact, a recent short-MMT study (i.e., a 4-day Templestay project, which consists in a four-day intensive mindfulness retreat based on Korean Buddhism) on naïve meditators was able to demonstrate a direct association between an improvement in executive control and increased activation in both the right ACC and the right dorsolateral prefrontal cortex (DLPFC) using the ANT[43]. The finding observed in the DLPFC is also supported by another study, in which an increased activation in the right DLPFC and decreased activation in the rostral prefrontal cortex (PFC) was observed in naïve-meditators after an 8-week, focused attention, MMT program[44]. The PFC, an essential brain area for executive functions including working memory, rule learning, planning, attention, and motivation[45], has therefore been demonstrated to be susceptible to exhibiting neuroplastic changes upon completing MMT. Moreover, several resting-state neuroimaging studies were able to determine that MMT increases the functional connectivity between the posterior cingulate cortex (PCC), dorsal ACC, and DLPFC[46–49].

Additionally, studies observing microstructural connectivity (i.e., white matter tracts) via diffusion tensor imaging (DTI) as well as regional grey matter volume via voxel-based morphometry were able to demonstrate neuroplastic changes as a consequence of engaging in MMT. For example, a recent MMT study found that naïve mediators, upon completing the eight-week mindfulness-based stress reduction (MBSR) training developed by Jon Kabat-Zinn[1], exhibited increased microstructural connectivity in the superior longitudinal fasciculus (SLF)[47], which is a white matter tract connecting the PCC and the DLPFC[50]. Other studies, in addition to observing changes in the SLF, observed increased connectivity between the corpus callosum and corona radiata, which are tracts connecting the ACC with diverse brain areas[51,52]. Furthermore, studies investigating gray matter structure observed volumetric changes in brain areas that play an important role in attention such as the PCC and hippocampus[53,54].

Interestingly, the hippocampus is another brain area particularly susceptible to both stress and MMT-induced connectivity- and volumetric changes[55–57]. In fact, prolonged, elevated, cortisol levels (i.e., a stress hormone) has been associated with lower hippocampal volume[58,59]. Chronic exposure to cortisol is known to cause neuronal damage particularly in the hippocampus; it also reduces synaptic connections and hippocampal neurogenesis, being presumably reflected in a decrease of hippocampal volume[60,61]. On the other hand, studies have observed larger hippocampal volumes in long-term meditators[62]. Moreover, a study investigating the role of the hippocampus in attention in children and adolescents found a significant correlation between increased hippocampal volume and improved auditory attention[63]. However, the association between the hippocampus, improved attention, and decreased stress levels as a result of MMT remains unknown.

It is important to note, that many of the previously mentioned MMT studies were provided with an in-person MMT, and not a web-based MMT as in the present study. In-person MMT tend to be very expensive, require a specific time commitment, and have a limited group capacity. Web-based MMT on the contrary offer a very flexible schedule, sessions that can be accessed multiple-times, a cost-effective training, and an unlimited number of participants can be included in the training. Due to technological development, and events such as COVID-19, research on web-based MMT is rising, and while initial research on web-based MMT demonstrates improved self-compassion, perceived stress, cognitive skills, mindfulness, and reduced anxiety and depression symptoms[64–67], there is a need of stronger and robust evidence, as the majority of these studies did not use an active control group to proof the efficacy of web-based MMT. Moreover, a recent review of MMT studies investigating effects on attention also highlighted the need of implementing active control groups to reliable study the effects of MMT, specifically, on attention[68]. Therefore, in the present work we used a study design that included an active control group to elucidate whether a web-based MMT can effectively reduce stress and anxiety levels, improve attention, states of mind, and physical well-being. Also, to the extent of our knowledge, this is the first neuroimaging study using a web-based MMT to identify attentional improvement mechanisms on the neuronal level. If successful, this could provide a larger portion of the population with a validated tool to improve their overall mental health and physical well-being.

The present study, therefore, sought to investigate the effects of a web-based MMT on attention and its association with changes in stress, anxiety, and flow state on both the behavioral and neuronal levels. To achieve this aim, this study utilized state-of-the-art magnetic resonance imaging (MRI) methods and robust statistical analyses procedures. The study had an active control group, pre- and post-intervention measurements (i.e., longitudinal study), and was registered as a clinical trial.

We hypothesized that the web-based MMT would elicit a reduction in stress and anxiety levels in addition to improvements in attention, perceived mindfulness, physical well-being, and flow experience. We expected to observe these behavioral changes accompanied by changes in brain function and structure in the form of increased activation in areas of the CC and PFC during the ANT and increased fractional anisotropy (FA) in white matter tracts connecting significantly activated areas seen in the ANT as a result of the web-based MMT.

Methods

Participants

Participants were mainly recruited at Klinikum rechts der Isar, Munich, Bayern, Germany via flyer distributions, online advertisements, and word-of-mouth. The study was advertised as a health-improvement program to ensure that participants were not aware of the mindfulness intervention during the recruitment or start of the experiment. Participants were recruited based on the following inclusion criteria: (1) No prior or current psychiatric or neurological conditions; screened for using the Mini-International Neuropsychiatric Interview (M.I.N.I)[69], (2) no psychotropic drugs use (including Cannabis), (3) meditation-naïve (i.e., participants should not have had more than three meditation sessions in the past year or more than ten meditation sessions over the course of their life), (4) right-handedness, (5) proficiency in the German language, and (6) age between 18 and 65 years. Additional exclusion criteria for the MRI sample were: (1) Pregnancy, (2) non-removable piercings, (3) tattoos on the head or neck, (4) metal parts or implants in the body, and (5) claustrophobia.

In a preliminary stage of the experiment, 19 participants were recruited for a pilot study to evaluate the effects of the web-based MMT on the behavioral level. Here, the effectiveness of the MMT on psychological outcomes, and cognitive function, specifically attention was observed. Following the completion of the pilot study, 72 additional participants were recruited to participate in the main, neuroimaging, study. For the main behavioural study (i.e., measurement of psychological outcomes) a total of 75 participants (43 females and 32 males; $\widetilde{age}$: 24 years, IQR (interquartile range): 13 years; $\widetilde{YOE}$ (years of education): 18 years, IQR: 5 years) were included. For the main study, flow experience was included as a psychological variable of interest. As this measurement was not added in the behavioural pilot, we were able to include only 57 participants (29 females and 28 males; $\widetilde{age}$: 30 years, IQR: 17 years; $\widetilde{YOE}$:18 years, IQR: 5 years) for the flow experience sample. Finally, for the main MRI study only 42 (22 females and 20 males; $\widetilde{age}$: 31.5 years, IQR: 17.2 years; $\widetilde{YOE}$:18 years, IQR: 5.62 years) out of 72 recruited participants survived the inclusion criteria. HT and MMT groups were not statistically different in age, gender, and YOE. More detail can be seen in Fig. 1 where a flowchart containing the demographics of the participants included in the pilot study, behavioral study, and fMRI study is depicted. All participants received monetary compensation for their participation.

Procedure

The study was registered as a clinical trial using the ISRCTN registry: trial ID ISRCTN95197731. Written informed consent was obtained from all participants and the study was approved by the ethics committee of Klinikum rechts der Isar, Technical University of Munich. Subjects were screened and scanned no more than 1 week prior to their first training session. All participants (in both the pilot and main study) completed a series of standardized questionnaires prior to- and upon completing the MMT or HT. The questionnaires were selected to assess stress levels (Perceived Stress Scale, PSS[70]), perceived mindfulness (Mindful Attention Awareness Scale –German version, MAAS[71,72]), anxiety levels (State and Trait Anxiety, STAI[73]), physical well-being (Fragebogen zur Erfassung des körperlichen Wohlbefindens, FEW-16[74]), and flow experience (Flow Short Scale, FSS[75]).

Participants in the imaging component of the main study were scanned on a 3T Philips Ingenia MR-Scanner (Philips Healthcare, Best, The Netherlands). During the scanning session, a series of neuroimaging sequences were acquired. During the fMRI sequence, participants completed an adapted, event-related, ANT to evaluate attention and its three attentional domains including the alerting, orienting, and executive control networks[76]. Following the pre-training assessment and scanning (TP1), participants were assigned to either the MMT or HT in a pseudo-randomized and single-blinded (subjects-only) manner. Once participants completed their assigned 31-day training program, they were asked to complete a post-training assessment (TP2) within two weeks following the end of their program. This post-training assessment consisted of the same questionnaires

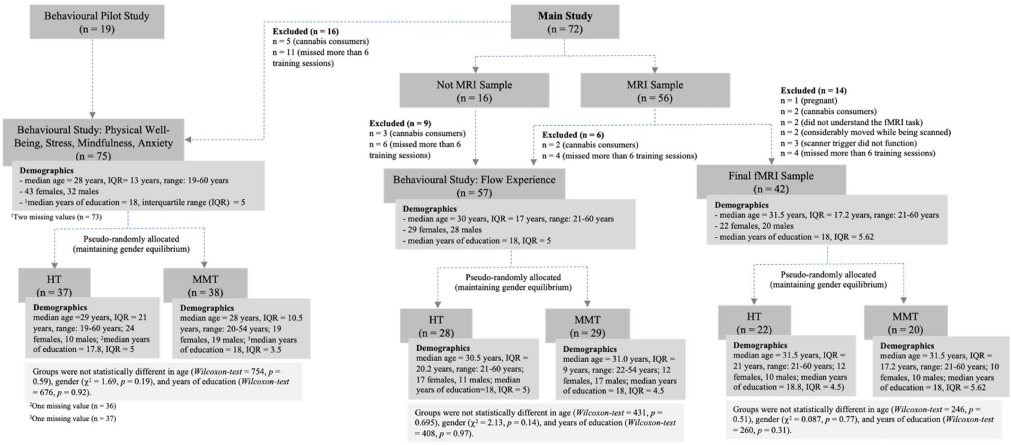


Figure 1. Demographics and statistics of study participants.

applied at TP1, and a second scanning session using the same protocol as TP1. During the TP2 assessment, participants were additionally asked about their compliance with the training program schedule. All participants (in both the MMT and HT groups) needed to complete at least 25 out of the 31 sessions to be included in the study. Enrollment in their respective training was confirmed using the training platform website (https://teachable.com).

Training

Both the MMT and HT were available online to study participants via the teaching platform www.teachable.com. Participants were given clear instructions on how to create a username to access free of cost their respective training. To ensure that only the content of the two training programs differed from one another, the training programs were structured in an identical manner, by means that both the MMT and the HT each presented a brief, 15-min, video every three days (starting on the first training day), followed by two days of 15-min podcasts or audio recordings. This pattern repeated for the duration of the 31-day course. Videos and audios were supported with written text providing participants with the most important information from the training session of the day. A detailed overview on the structure and content of both the MMT and HT can be found in the supplemental materials (S1).

Mindfulness meditation training

The MMT utilized in this study was based on the MBSR program and developed free of charge in close cooperation with Dr. Britta Hölzel (BKH), an MBSR instructor and mindfulness researcher, and contains guided mindfulness meditations and exercises, in addition to theoretical concepts and explanations provided in German by BKH. More specifically, theoretical topics included mindfulness research, mind wandering, body awareness, stress physiology, dealing mindfully with pain and difficult emotions, loving kindness, self-perception, connectedness, and others. Guided meditations instructed participants to focus on various objects of attention, such as the breath, body sensations, emotions, thoughts, and walking, in addition to encountering these experiences without judgment, with acceptance, and with kindness. Loving kindness and open monitoring practice were also included.

Health training

The HT was developed as an active control training program that closely resembled the structure of the MMT but instead gave information on topics pertaining to everyday health. It is important to note that the HT did not contain any information or active training related to mindfulness meditation or meditation in general. Instead, the HT provided participants with health-related topics such as sleep, burn-out, aging, pain, and nutrition.

Attentional network test

The ANT is a paradigm that assesses different forms of attention (i.e., alerting, orienting, and executive control). An adapted version of the ANT was used during the event-related fMRI sequence to observe the neuronal activation patterns of these attentional networks. The ANT consisted of three cue conditions (no cue, center cue, spatial cue) and two target conditions (congruent target, and incongruent target). The no cue condition (i.e., the baseline condition) consisted of a fixation cross presented in the center of the screen. The center cue condition consisted of a fixation cross with an asterisk overlaid in the center of the screen; the function of the center cue condition was to alert participants about the onset of the upcoming target stimulus. The spatial cue condition consisted of an asterisk displayed on either the left or right side of the side of the screen; the function of the spatial cue condition was to orient the attention of the participant to the direction of the upcoming target. Each cue condition had a duration of 200 ms. The cue condition was then followed by one of two target conditions (the congruent or incongruent conditions). The target conditions consisted of a column with 5 horizontal arrows pointing either leftward or rightward. The objective of this condition was for the participants to determine the direction of the center arrow. In congruent conditions, all arrows pointed in the same direction, whereas in the incongruent condition, the center arrow pointed in the opposite direction, thereby introducing a response conflict. Reaction times (RTs) to target conditions were measured. Participants were instructed to use either the index- or middle finger of their right hand to indicate via a button-press whether the center arrow was pointing to the left or right, respectively. The experiment consisted of two runs each comprising of 36 trials. A full trial is depicted in Fig. 2. Congruent and incongruent conditions were counterbalanced and randomly generated. The ANT paradigm for the fMRI session was programmed and presented to the participants using the Presentation* software (Version 20.1, Neurobehavioral Systems, Inc., Berkeley, CA, United States, www.neurobs.com).

Acquisition of MRI data

All MR imaging was performed on a 3T Philips Scanner, equipped with a 32-channel head coil at Klinikum Rechts der Isar in Munich, Germany. Whole brain functional scans, with 63 anterior commissure—posterior commissure (AC-PC) axial slices (0.2 mm interslice gap) were acquired using a T2*-weighted 2D single shot gradient-echo echo-planar imaging (GE-EPI) sequence, multi-band (MB) Factor = 3, echo time (TE) = 33 ms, repetition time (TR) = 1550 ms, flip angle = 70°, field of view (FOV) = 192 × 192 × 138.4 mm^3, and an 8 mm^3 isotropic voxel resolution. The total ANT-fMRI acquisition time was 13 min. To estimate the corresponding field maps to correct for EPI-distortions[77], two T2*-weighted images were acquired using a gradient echo sequence with two different TE lengths (long TE = 10.54 ms, short TE = 6.0 ms); here, the FOV, spatial resolution, and number of slices were the same as for the functional scans. Structural scans were acquired, with 230 AC-PC axial slices (0.7 mm interslice gap) using a T1-weighted MPRAGE sequence with TE = 5.2 ms, TR = 11 ms, flip angle = 8°, FOV = 256 × 240 × 161 mm^3, and a voxel resolution of 0.7 × 0.7 × 0.7 mm^3. For DTI, diffusion-weighted images (DWI) were acquired with a TR = 5643 ms, TE = 96 ms, FOV = 224 × 256 × 132 mm^3, and an isotropic voxel resolution of 2 mm. Diffusion-sensitizing gradient echo encoding was applied in 64 directions using a diffusion-weighting factor (*b*) of 1400 s/mm^2. The total DWI acquisition time was 8 min. The following sequences were additionally acquired during the imaging protocol: Fluid-attenuated inversion recovery (FLAIR, for clinical purposes), resting-state fMRI, and pseudo-continuous arterial spin labeling (pCASL, to evaluate MMT effects on cerebral perfusion). Results of the resting-state fMRI and perfusion study are reported in[49] and[78], respectively .

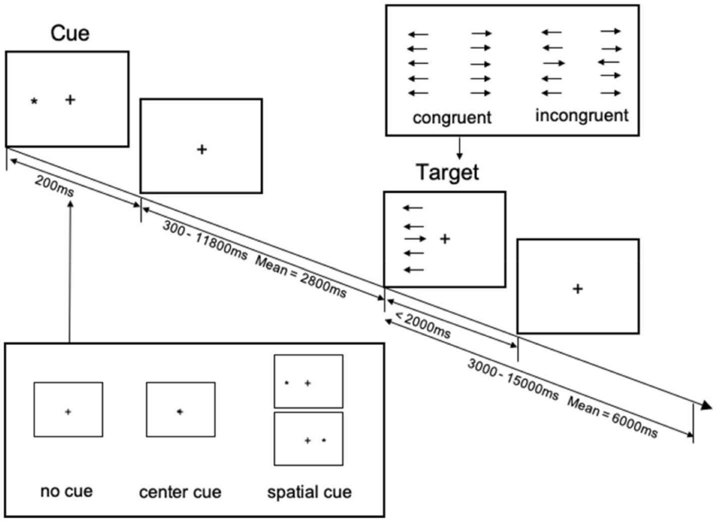


Figure 2. This figure depicts a simplified version of the ANT. Arrows were presented in a column on either the right or left side of the screen. Here, it is important to note that the arrangement of the arrows deviated from the traditional ANT paradigm, such that the arrows were presented in a vertical column, as opposed to in a horizonal row. This was done as in-house pilot experiments indicated a greater effect in the orienting network of attention when the arrows were presented in the vertical arrangement. This figure was adapted from[76].

Analysis of DTI data

The DTI data was first denoised using the *dwidenoise* algorithm from MRtrx3[79]. The ExploreDTI software[80] was used to conduct signal drift correction, Gibbs ringing correction, Venetian Blinds correction, motion, and EPI/eddy current distortion corrections. The preprocessed images were subsequently fitted to the constrained spherical deconvolution (CSD) model at each voxel[81,82]. FA maps of the white matter tracts of interest were calculated and extracted using the automated/atlas-based region of interest (ROI) analysis of Explore DTI. The tracts of interest were selected based on the significant activations observed in the group-by-time interaction in the fMRI data from the ANT. These tracts included the SLF and the right uncinate fasciculus (rUNC). The atlas "JHU ICBM-DTI-81 White-Matter Labels"[83] implemented in the ExploreDTI software was used to extract the FA values of the tracts of interest. To observe the group-by-time interaction effects, a two-way mixed ANOVA (with group as the between-subjects factor and time as the within-subjects factor) was conducted on the FA values of the SLF and rUNC. Statistical analyses were conducted using R[84]. Multiple comparison corrections were applied using the Bonferroni method[85]. Statistically significant changes in FA were visualized using raincloud plots[86]. To visualize an example of the white matter tracts of interest, CSD-tractography in manually selected ROIs was done on a control and an experimental participant using Explore DTI.

Analysis of event-related functional MRI data

Preprocessing and voxel-based analysis of the functional images were conducted using statistical parametric mapping (SPM12, The Wellcome Centre for Human Neuroimaging, London, UK). Participants with a framewise displacement ($FD_{mean} > 0.25$) were excluded[87,88]. Our pipeline to preprocess the data was as follows: Realignment to the mean functional imaging and unwarping of fMRI time-series, co-registration of anatomical MRI to mean functional image, segmentation of anatomical images, creation of a group-specific DARTEL template[89] for normalization purposes, normalization to MNI space, and smoothing with a 4 mm FWHM Gaussian Kernel. Slice time correction was not performed as a multiband sequence was used to acquire the data and the TR used was less than 2 s, making the acquisition robust enough to avoid slice timing problems[90].

Based on the general linear model, a canonical hemodynamic response function was convolved on the event onset-times within the time series to create a statistical model of the ANT for each subject. Design matrices of the first level analysis consisted of five regressors: no cue (i.e., fixation cross), center cue, and spatial cue, in addition to the congruent- and incongruent targets. Six additional nuisance regressors pertaining to movement translations (x,y,z) and rotations (rx, ry, rz) were added to the design matrix. The second level analysis was performed using a two-way repeated measures full factorial ANOVA on the contrasts of interest: alerting network (center cue—no cue), orienting network (spatial cue—center cue), and executive attention network (incongruent target—congruent target). The height (intensity) threshold was set to uncorrected $p = 0.05$. Multiple comparison correction at $p < 0.05$ was determined by a Monte Carlo simulation yielding a cluster size threshold of 350 voxels ($2 \times 2 \times 2$ mm^3). The parameters of the simulation were as follows: SPM volume in voxels ($x = 64$, $y = 77$, $z = 50$), local $p = 0.05$, one tail, global $p = 0.05$, fwhm = 2 voxels, number of iterations = 1500, *t*-distributed, $df = 80$, number of maps = 3 (https://github.com/mbrown/fmrimontecluster/blob/master/fMRIMonteCluster.m by Grown, M. R. G. 2013). Parameter estimates of the activated clusters were obtained using MarsBaR[91]. 3D visualizations of fMRI images were created following the Madan[92] Guide.

Behavioral data analyses

Training effects on the attentional networks were assessed using three three-way mixed ANOVAs on the RTs of the ANT, as seen in[43], with time (TP1 and TP2) and network conditions as the within-subject factors (i.e., no cue and center cue for the ANOVA of the alerting network condition; center cue and spatial cue for the ANOVA of the orienting network condition; congruent and incongruent target for the ANOVA of the executive network condition), and group (MMT and HT) as the between-subject factor. Effects on anxiety, stress levels, mindfulness, flow experience, and physical well-being were assessed by two-way mixed ANOVAs. Data distributions of the behavioral questionnaires are visualized in raincloud plots[86]. Effect sizes were calculated using Cohen's *d* (Eq. (1)). Statistical analyses were conducted using R[84].

$$Cohen's\, d = \frac{\mu}{\sigma \sqrt[2]{1 - r}},\ where\ \mu = \overline{RT_{TP1} - RT_{TP2}}\quad RT = Reaction\ Time,\ TP = Time\ Point \tag{1}$$

Correlation between brain activation, ANT, and psychological outcomes

Based on our research interest and on the statistically significant behavioral results (i.e., the observed reduced stress and anxiety levels, and increased flow state after the MMT intervention), Pearson's correlations (*r*) between (a) PSS and ANT-Reaction times, (b) PSS and brain activations, (c) ANT alerting network effect (center cue RT—no cue RT) and brain activations, (d) trait anxiety and brain activations, and (e) flow experience and brain activations were assessed. Pearson's correlations were corrected for multiple comparisons using the Holm method[93]. Python programming language (Python Software Foundation, https://www.python.org/) was used to perform correlation analysis.

Ethics approval

The study protocol was approved by the ethics committee of Klinikum rechts der Isar, Technical University of Munich.

Informed consent
Written informed consent was obtained from all individual participants in the study.

Results
Standardized questionnaires results
When conducting a two-way mixed ANOVA on trait anxiety we were able to observe a significant group-by-time interaction ($F(1,68) = 5.52$, $p = 0.02$). Post-hoc paired *t*-tests confirmed a significant decrease in trait anxiety ($t(35) = 3.29$, $p = 0.002$) with a large effect size (Cohen's $d = -1.30$) in the MMT group; this significant decrease was not observed in the HT group ($t(34) = 0.80$, $p = 0.43$, Cohen's $d = -0.28$). It is important to note that the baseline value for trait anxiety was statistically different between the MMT and HT groups ($t(73) = 2.33$, $p = 0.02$) (Fig. 3a).

While the perceived stress questionnaires did not yield significant group-by-time interaction when conducting the two-way mixed ANOVA, we were, however, able to observe a significant decrease in stress levels in the MMT group at the second time point (TP2) ($t(36) = 2.25$, $p = 0.03$, Cohen's $d = 0.46$), whereas no significant decrease in stress levels were observed in the HT group at TP2 ($t(36) = 1.20$, $p = 0.24$, Cohen's $d = 0.06$) (Fig. 3b).

Additional behavioral measures of interest were mindfulness and flow. The two-way mixed ANOVA of the MAAS did not yield a significant interaction ($F(1,71) = 1.120$, $p = 0.3$) (Fig. 3c). A significant group-by-time interaction was, however, observed for the two-way mixed ANOVA of flow experience ($F(1,51) = 9.254$, $p = 0.004$). Post-hoc paired t-tests demonstrated a significant increase in flow experience for the MMT group ($t(24) = -4.56$, $p = 0.0001$) with a large effect size (Cohen's $d = 1.46$), which was not observed in the HT group ($t(27) = -0.09$, $p = 0.93$, Cohen's $d = 0.04$). It is important to note that the baseline value for flow experience was statistically different between the MMT and HT groups ($t(51) = -3.24$, $p = 0.002$) (Fig. 3d).

For our final measurement of interest, physical well-being, a moderate effect size (Cohen's $d = 0.52$) was observed indicating an improvement in perceived physical well-being in the MMT group; however, this result was not statistically significant. No effect was observed in the HT group (Cohen's $d = 0.13$) (Fig. 3e).

ANT reaction times results
Interestingly, the mean overall RT significantly improved by ~ 48 ms ($t(1,19) = 5.07$, $p = 0.00008$) in the MMT group at TP2, whereas the mean RT for the HT only decreased by ~ 23 ms, which was not statistically significant ($t(1,22) = 1.10$, $p = 0.285$) (Fig. 4). These results indicate that there was more than a two-fold RT improvement in the MMT group compared to the HT group. Despite these striking results for overall RT, this effect was not specific when considering the individual RTs of the three attentional conditions (i.e., the alerting-, orienting-, and executive- conditions) and conducting a three-way mixed ANOVA for each of them, with group as a between-subjects factor, time and condition as within-subject factors, yielded no significant group-by-time-by-condition interaction across the different conditions.

In the following, all significant interactions are reported for a complete overview of the finding. A significant two-way interaction ($F(1,39) = 6.811$, $p = 0.01$) between group (i.e., MMT and HT) and condition (i.e., center cue and spatial condition) for the orienting condition of attention was observed. The post-hoc two-way ANOVA analysis revealed a significant main effect of group in the spatial cue condition ($F(1,163) = 4.84$, $p = 0.03$), indicating that the MMT group demonstrated faster spatial cue RT at baseline and at TP2. As expected, a main effect of condition for alerting (no cue and center cue) ($F(1,39) = 11.097$, $p = 0.002$) and executive attention (incongruent and congruent) ($F(1,40) = 34.39$, $p < 0.001$) was observed, indicating that, when the condition was more cognitively effortful (i.e., complex) the reaction time increased. Furthermore, and not surprisingly, main effects of time were observed for each attentional condition ($F(1,39)_{\text{Alerting}} = 16.469$, $p < 0.001$; $F(1,39)_{\text{Orienting}} = 21.16$, $p < 0.001$; $F(1,40)_{\text{Executive}} = 15.53$, $p < 0.001$), indicating practice effects from the first to second testing timepoints.

As seen by the effect sizes for the change in RT in each group (Table 1), the effects of the intervention were not specific to a particular attentional condition, indicating that, the RTs significantly improved for the MMT group in all attentional conditions, and did not have an effect on any particular attentional network.

fMRI results
To determine whether there was a significant change in brain activation during the ANT at TP2 as a result of the MMT, a whole brain, two-way, repeated measures full factorial ANOVA was conducted (Table 2). This analysis demonstrated a significant group-by-time interaction during the alerting condition in which an increase in activation in the left superior frontal gyrus (SFG; $p_{FWE} = 0.003$, $p_{monte\text{-}carlo} < 0.001$), Brodmann area 31 (BA 31; $p_{FWE} < 0.001$, $p_{monte\text{-}carlo} < 0.001$), and the right hippocampus ($p_{\text{FWE}} = 0.240$, $p_{monte\text{-}carlo} = 0.001$) in the MMT group (in comparison to the HT group) was observed. Figure 5 illustrates the significantly activated clusters from the group-by-time interaction, and Fig. 6 depicts the change in parameter estimates (β values) of the brain areas exhibiting increased activation in the MMT group via boxplot visualizations. Interestingly, we were also able to observe decreased activation (also visualized in the boxplots of the parameter estimates) in the HT group. The other attentional conditions (i.e., orienting, and executive attention) did not yield significant group-by-time interaction results.

DTI results
To determine whether the changes observed in brain activation during the ANT were accompanied with micro-structural changes in the white matter of the brain, we conducted a DTI analysis on two fiber tracts, namely the right uncinate fasciculus (a tract that connects the PFC with the right hippocampus), and the SLF, a tract that connects the PCC (i.e., BA31) with the PFC. These fiber tracts were selected as they are associated with the significant brain area activations observed during the ANT. The DTI results, through a group-by-time two-way mixed

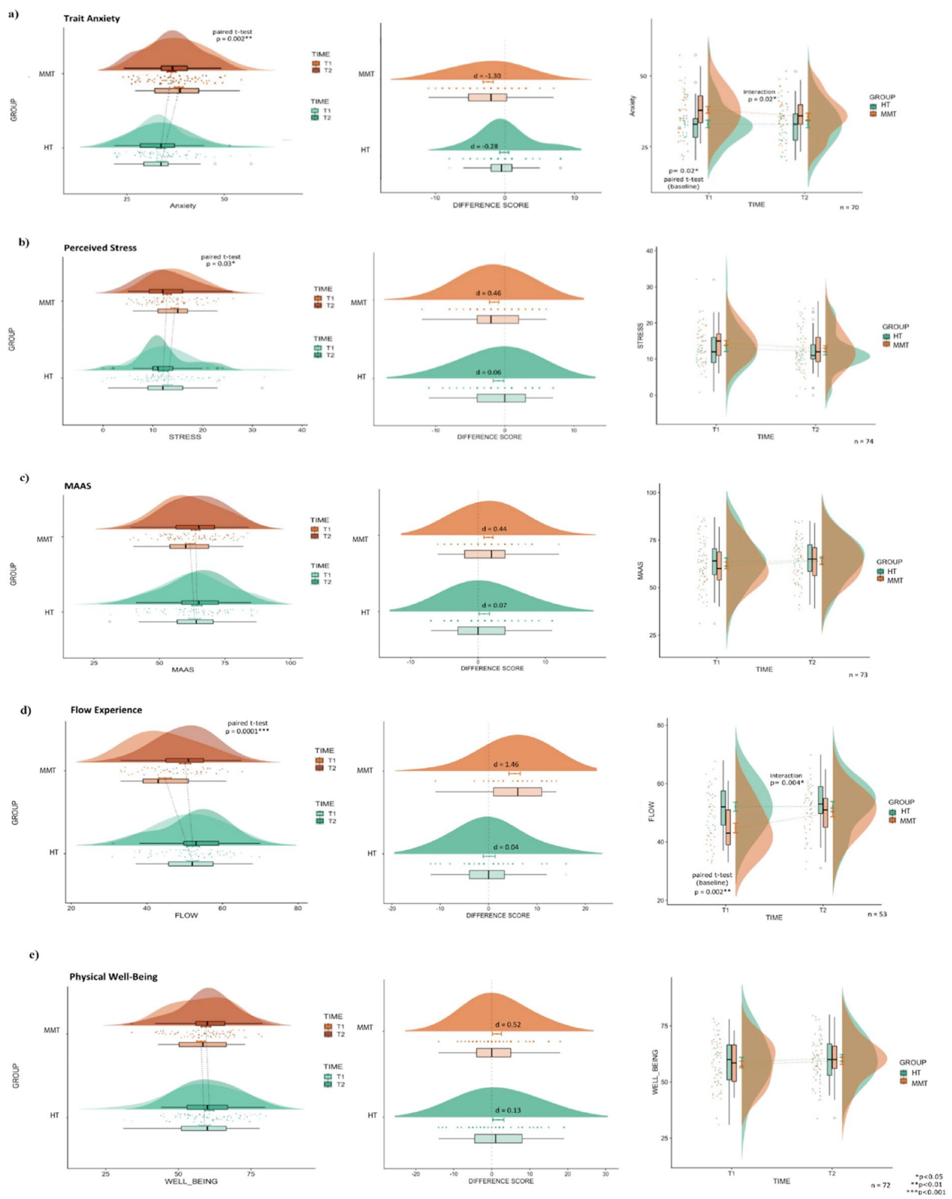


Figure 3. Results of trait anxiety, perceived stress, MAAS (i.e., mindfulness), flow, and physical well-being questionnaires are presented in Rain-Cloud Plots. Significant *p*-values (*p*), Cohen's *d* effect sizes (*d*), and sample size (*n*) are shown.

ANOVA, were able to demonstrate a significant training-associated increase in FA in the rUNC (F(1,42) = 6.047, p = 0.018) in the MMT compared to the HT group (Fig. 7); these results survived Bonferroni correction. The group-by-time two-way mixed ANOVA analysis for the DTI results in the SLF yielded no significant interaction.

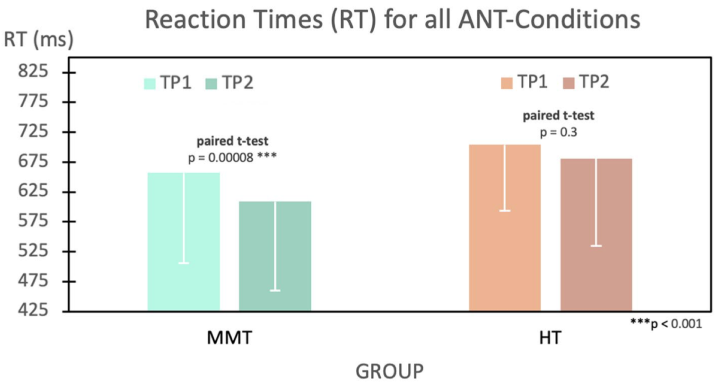


Figure 4. Mean reaction times (mean ± SD) in ms of the MMT and HT groups before and after the intervention over all conditions.

Cue	Target	Cohen's *d*	
		HT	MMTs
No	Congruent	0.24	2.3
	Incongruent	0.40	3.2
Center	Congruent	0.46	3.1
	Incongruent	0.26	3.3
Spatial	Congruent	0.78	1.4
	Incongruent	0.43	3.9

Table 1. ANT effect sizes for the difference in RT between the two timepoints for each group. The Cohen's *d* (*d*) effect size scale is: negligible effect ($d < 0.2$), small effect ($0.2 \leq d < 0.5$), moderate effect ($0.5 \leq d < 0.8$), and large effect ($d \geq 0.8$)[94,95].

Region	MNI coordinates (mm)			Cluster-level		
	x	y	z	$p_{FWE\text{-}corrected}$	$p_{monte\text{-}carlo\text{-}corrected}$	k^a
Superior Frontal Gyrus Left	− 12	44	46	0.003	< 0.001	1054
Brodmann Area 31	12	− 48	36	< 0.001	< 0.001	1992
Right Hippocampus	34	− 36	− 8	0.240	0.001	484

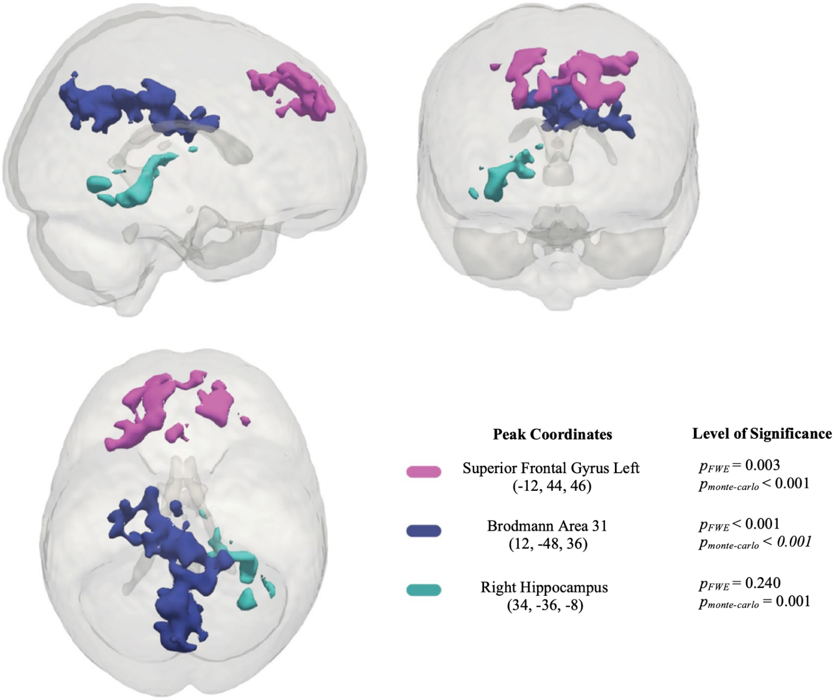
Table 2. Regions showing a significant group-by-time interaction for the alerting network of the ANT (no cue—center cue). $^a k$ = cluster size in voxels.

Correlations: brain activations in the alerting condition, ANT reaction times, and psychological outcomes

An additional aim of this study was to determine the relationship between the neuroplastic and behavioral (i.e., psychological) changes upon completing the MMT; correlation analyses between the increased training-related brain activations in the ANT during the alerting condition (i.e., SFG, Brodmann Area 31, and right hippocampus) and behavioral measures (i.e., PSS, ANT RTs, trait anxiety, and flow experience) were therefore conducted.

The correlation analysis between perceived stress levels and the increased brain activations observed in the ANT yielded a significant negative correlation ($r = -0.51$, $p = 0.02$, Fig. 8) between PSS scores and the activation in the right hippocampus after MMT that marginally survived the Holm's correction method for multiple comparisons. This correlation was not observed in the MMT group before the intervention nor in the HT at any of the two time points (Table 3). An additional correlation analysis was conducted to observe whether there was an association between the change in PSS scores and the change in mean ANT reaction time in the MMT group (TP2 vs TP1). This correlation approached significance ($r = 0.36$, $p = 0.059$, one-tailed).

We were also interested in determining whether we could observe a relationship between the alerting effect (no cue—center cue) and the significant brain activations, but no significant correlations were found. However,



	Peak Coordinates	Level of Significance
🟪	Superior Frontal Gyrus Left (-12, 44, 46)	$p_{FWE} = 0.003$ $p_{monte\text{-}carlo} < 0.001$
🟦	Brodmann Area 31 (12, -48, 36)	$p_{FWE} < 0.001$ $p_{monte\text{-}carlo} < 0.001$
🟩	Right Hippocampus (34, -36, -8)	$p_{FWE} = 0.240$ $p_{monte\text{-}carlo} = 0.001$

Figure 5. Neuroimaging results in MNI space of the two-way repeated measures, full factorial, ANOVA for the alerting network of attention. This figure shows the significant brain activations when comparing the MMT and HT groups.

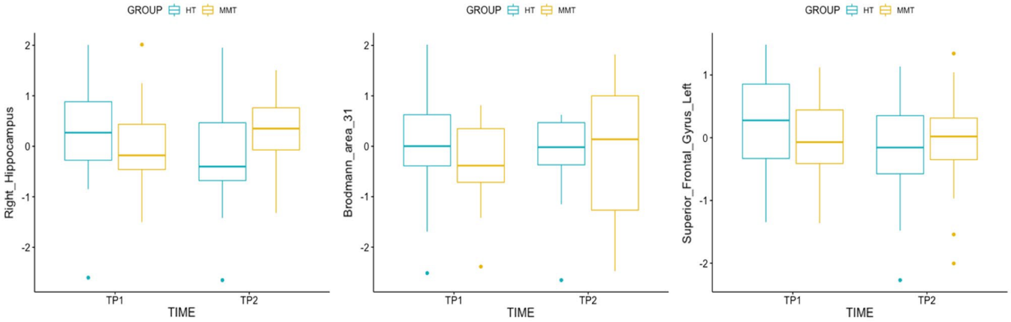
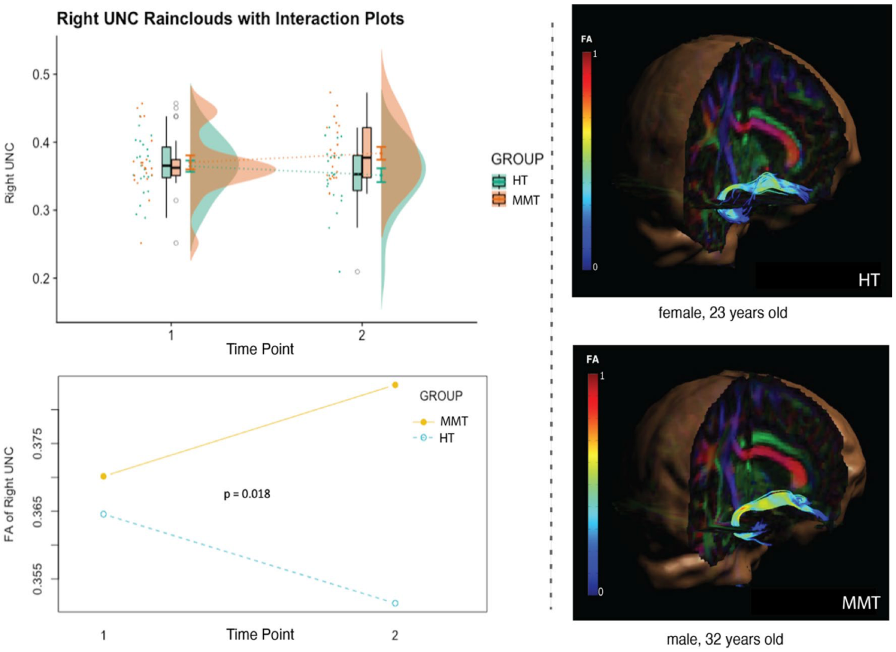


Figure 6. Parameter estimate boxplots illustrating the directionalities of activation in the right hippocampus, Brodmann area 31, and left superior frontal gyrus in both the MMT and HT at each time point.

a trending, positive, correlation ($r = 0.4$) between the change in activation in the SFG and the change in reaction times of alerting cue (i.e., center cue) was observed ($p = 0.08$).

Another correlation of interest within the scope of this study was to determine the relationship between trait anxiety levels and the observed brain activations. The correlation analysis yielded a significant negative correlation ($r = -0.46$, $p = 0.04$) between the trait anxiety scores and the activation in the right hippocampus in the MMT group at TP2. Interestingly, we were also able to observe a significant positive correlation in the HT group at TP1 ($r = 0.52$, $p = 0.02$). No significant correlations were observed in the MMT at TP1 nor were any correlations observed in the HT group at TP2. However, it is important to note that the positive correlation observed in the HT group at TP1 only marginally survived Holm's correction for multiple comparisons, while



female, 23 years old

male, 32 years old

Figure 7. On the left, the change in FA values in the rUNC of the HT and MTT groups is depicted by raincloud and interaction plots. On the right, examples of the tractography of the rUNC of a HT and MMT participant are depicted.

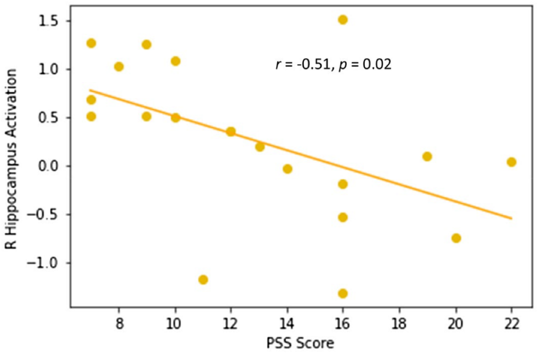
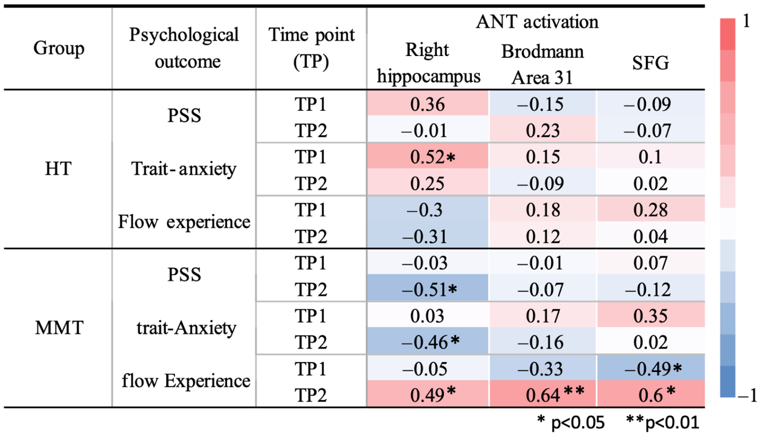


Figure 8. This plot depicts the correlation between the PSS scores and the right hippocampus activation (β values) after completing the MMT (TP2).

the negative correlation in the MMT group at TP2 did not. No significant correlations were found between trait anxiety and the SFG, nor between trait anxiety scores and the Brodmann Area 31 (Table 3).

Our final correlation of interest was to observe the relationship between flow state and the increased brain activations. The correlation analysis yielded significant, positive, correlations in the MMT group at TP2 between flow experience and the right hippocampus activation ($r=0.49$, $p=0.047$), Brodmann area 31 activation ($r=0.64$, $p=0.006$), and SFG activation ($r=0.6$, $p=0.01$). No significant correlations were observed in the MMT group at TP1 nor in the HT group at TP1 or TP2 (Table 3). All significant correlations observed in relation to flow experience survived the Holm´s multiple comparison correction.



Group	Psychological outcome	Time point (TP)	ANT activation		
			Right hippocampus	Brodmann Area 31	SFG
HT	PSS	TP1	0.36	−0.15	−0.09
		TP2	−0.01	0.23	−0.07
	Trait-anxiety	TP1	0.52*	0.15	0.1
		TP2	0.25	−0.09	0.02
	Flow experience	TP1	−0.3	0.18	0.28
		TP2	−0.31	0.12	0.04
MMT	PSS	TP1	−0.03	−0.01	0.07
		TP2	−0.51*	−0.07	−0.12
	trait-Anxiety	TP1	0.03	0.17	0.35
		TP2	−0.46*	−0.16	0.02
	flow Experience	TP1	−0.05	−0.33	−0.49*
		TP2	0.49*	0.64**	0.6*

* p<0.05 **p<0.01

Table 3. Correlations observed between the psychological outcomes (PSS, trait anxiety, and flow experience) and the training-related increased brain activations (right hippocampus, Brodmann area 31, and SFG) in the HT and MMT group for both TP1 and TP2.

Discussion

The main aim of the present study was to investigate the effects of a 31-day web-based MMT on attention on both the behavioral and neuronal levels and its relationship with changes in perceived stress, trait anxiety, and flow experience. Through the use of robust analysis methods, the results of this study demonstrated that a brief web-based MMT led to improvements in the behavioral measures of mental health (i.e., reductions in trait anxiety and stress levels), states of mind (i.e., flow experience), attentional performance (i.e., reaction-time improvements), and to significant neuroplastic changes exhibited by an increase in brain activation in the superior frontal gyrus, Brodmann area 31 (i.e., PCC), and right hippocampus during the alerting condition of the attentional task. These results were corroborated by changes observed in the microstructural integrity between the right hippocampus and the superior frontal gyrus (i.e., FA changes in the right uncinate fasciculus). We were able to observe these significant changes on both the behavioral and neuronal levels, and to associate the neuronal changes to our observed improvements in attention as well as to reductions in stress and trait anxiety. Our findings, therefore, contribute to the research conducted on possible interventions for chronic stress, an ever-increasing central health issue.

One of our main findings of interest demonstrated significant MMT-elicited improvements in cognitive and executive functioning, specifically attentional performance. We were able to demonstrate improvements in the overall RT during the ANT and to observe an increase in brain activation in the superior frontal gyrus, PCC, and right hippocampus during the alerting condition of the ANT. These neuronal findings are noteworthy given their association with cognitive and executive functioning seen in previous literature findings. For example, the PCC has been attributed to playing a crucial role in cognitive functioning, specifically with regard to the RT of cognitive performance, and it has been associated with the frontoparietal control network as well as the dorsal attention network, which are both critically involved in visuospatial attention[96–98]. Our results observed in the PCC, therefore, continue to support previous findings reported in the literature.

Interestingly, as the PCC has been demonstrated to be a major node in multiple intrinsic connectivity networks it is directly associated with the hippocampus, ACC, and PFC[96]. Like the PCC, the hippocampus is an important brain region involved in visuospatial attention[99]. More specifically, the dorsal hippocampus plays a role in cognitive functioning, while the ventral hippocampus modulates behavioral adaptation to stress[100]. Our findings observed in the right hippocampus, therefore, support the findings in the literature, while also continuing to emphasize the role the hippocampus plays in cognitive functioning and attention. Similarly, the ACC is a brain region involved in executive functioning and has also been implicated in the effects of mindfulness meditation[39,43,101]. In fact, evidence supports that experienced meditators exhibit increased connectivity between the PCC, ACC, and DLPFC[46] which are brain areas attributed to cognitive functioning and are also susceptible to the effects of MMT[47,102–104]. In addition, MMT studies conducted on naïve-meditators have also shown an increased resting-state PCC-DLPFC connectivity. The DLPFC, formed by the lateral part of the SFG and middle frontal gyrus[105], plays an important role in focused attention[106]. Moreover, our observed activations in the SFG, can be linked to previous findings in which the SFG activations were attributed to higher cognitive functioning and, more specifically, to attentional shifting and spatial cognition[107,108]. In fact, patients with attention-deficit/hyperactivity disorder (ADHD) have shown abnormal function and structure in the SFG[109]. Additionally, a study done on an epileptic patient, where activity in the SFG was recorded with subdural electrodes, demonstrated via the Flanker Task (an attention task similar in nature to that of the ANT) that the SFG actively participates in executive control tasks[110]. Therefore, our trending toward significant correlation observed in the MMT group between the increased SFG activation and faster RTs in the alerting condition of the ANT, is in line with this interpretation thus continuing to emphasize the important role MMT can have on improving attention.

Interestingly, we were able to observe both improvements in cognitive functioning as represented in the decrease in RTs during the ANT and a significant group-by-time interaction showing an increase in flow experience in the MMT. These findings are important as it implies that MMT can have an effect on both attentional mechanisms, as well as on the psychological flow state. While the research conducted on flow is still considered to be a relatively new line of research[111], the neuroimaging results observed in the present study are able to provide initial insight into the association between increased flow and neuroplastic changes through the observed correlation between flow-experience and brain activation in the right hippocampus, PCC, and SFG, during the ANT. This finding, therefore, emphasizes the important relationship between mindfulness, attentional functioning, and flow experience.

Although no significant group-by-time interaction was observed in perceived stress, we were able to demonstrate a statistically significant reduction in the MMT group in stress level (observed via the PSS), not seen in the HT group. It is important to note, that we may not have been able to observe an interaction for the PSS due to the low perceived stress at baseline for both the MMT and HT groups. Therefore, the null result in the group-by-time interaction should be considered with caution, especially when previous research demonstrated MMT's ability to elicit greater stress reduction in individuals with higher initial stress than participants with lower initial stress levels[112].

We were also able to demonstrate a negative correlation between hippocampal activation and the PSS score in the MMT group at TP2 (Fig. 8). This finding is significant given the role of the hippocampus in modulating the behavioural adaptation to stress[100]. In fact, previous research has been able to demonstrate a decrease in activation in brain areas associated with the limbic system (i.e., hippocampus, hypothalamus, medio orbitofrontal cortex, and ACC) during acute stress, triggered by an increase of cortisol levels[113], while also demonstrating that MMT can have an influence on both the functional and structural changes in the hippocampus[53,57,114,115]. Our previous study utilizing voxel-based morphometry to observe MMT-elicited neuroplastic changes, demonstrated greater gray matter concentration in the right hippocampus of meditators[116], further emphasizing the importance of the increase in hippocampal activity observed in our functional imaging data. We were able to demonstrate an association between trait anxiety, perceived stress, and hippocampal activity during an attention task, and that MMT can have an influence on the white matter microstructure of the brain by means that we observed increased FA in the rUNC. These results indicate that MMT strengthened the connection between the hippocampus and areas of the frontal lobe. In fact, our findings replicate the results of our previous DTI study in which a significant increase in FA in the right UNC following MMT was detected[117]. Other studies have also demonstrated an increase in FA of white matter tracts surrounding the dorsal part of the hippocampus[118], in addition to associating changes in the left UNC with the experience of silence in a different form of meditation[119]. Our results demonstrating MMT-related activations in the hippocampus and increased FA in the rUNC, taken together with the finding in the literature, suggests a close relationship between structural and functional changes in specific brain regions and, more specifically, that the hippocampus may be a candidate to mediate the relationship between MMT, attention, and stress reduction.

It is, however, important to consider the limitations that accompany the scope of this study. For example, while previous studies demonstrated the effectiveness of a brief MMT on behavioral measures, additional studies were able to demonstrate that psychological outcomes can be positively moderated by the number of MMT hours conducted[2,120]. Therefore, as our MMT was one month shorter in comparison to the standard MBSR program[3], we expect that by increasing the duration of our web-based MMT, larger effects could be reached. Nevertheless, our findings indicate that engaging in brief web-based MMT can also elicit significant behavioral and neuroplastic changes and is therefore a significant contribution to the literature.

An additional limitation to consider is the small sample size of our neuroimaging data, as it was challenging to find meditation-naïve, MRI suitable participants. And, given the longitudinal nature of this study, we also had an attrition rate of ~ 10%. Moreover, technical issues with the MRI scanner or excessive motion during the scan reduced our sample size. Another disadvantage in our study design was the inability to prove participant compliance in the web-based training programs.

Furthermore, the participant sample in this study exhibited a non-normal distribution for age; this, in turn, may have influenced the observed results, given the differences between the older and younger participants. In fact, previous studies have already reported differences in the impact of MMT between different age groups[121,122]. Nevertheless, the results of this study ultimately contribute to the understanding of the neural mechanisms of MMT on attention, in addition to its impact on psychological outcomes. Future studies should investigate the use of the current web-based mindfulness training in clinical populations in an effort to observe similar results on stress, anxiety, and cognitive capacities.

Conclusion

This was a complex longitudinal, web-based MMT study involving acquisiton of several MR neuroimaging data, including event-related fMRI and DTI, and assessment of psychological outcomes by means of stadardized questionnaires. These data combined with the inclusion of an active control group successfully and reliably demonstrated that a short web-based mindfulness training has the potential to improve mental health (i.e., by reducing anxiety and perceived stress levels), cognitive performance (i.e., attention mechanisms), and state of mind (i.e., flow experience), which coincide with alterations in underlying brain structure (i.e., increased FA in the rUNC), and brain function (i.e., increased activation in the PCC, right hippocampus, and SFG). These findings provide the scientific community with valuable insight into the relationship between mindfulness training, mental health, cognitive function, and its corresponding neural correlates. More specifically, we showed that the decrease in stress and anxiety in our experimental group is presumably a precursor of improved hippocampus function, reflected in improvements of alerting attention. And finally, this increase in functionality might have caused white matter changes in the rUNC which connects the right hippocampus with frontal areas of the brain known to be involved in attentional processes.

We were also able to demonstrate an important link between the mindfulness meditation training-related increase in flow experience and the SFG, right hippocampus and PCC, which as previously described are important brain areas involved in attentional processes. Furthermore, a recent publication by Xie[123] was able to demonstrate an association between flow experience, mindfulness, and team-working abilities. The study reported a correlation indicating that productivity was associated with higher mindfulness and flow experience levels. Given these findings, our results may indicate that the web-based MMT used in our study may be suitable for companies and their employers due to its ability to increase flow experience and attention. Previous literature have also suggested a link between mindfulness, flow, and higher workplace performance[124]. Web-based MMTs could, therefore, be beneficial to companies and their employers by increasing workflow experience, and may also help to decrease the stress and anxiety elicited by a stressful workday. As stress and anxiety have been demonstrated to impair cognitive performance and function[125], MMTs, by decreasing stress and anxiety levels, help to improve overall cognitive function (i.e., attention), thereby improving productivity.

In conclusion, web-based MMT could serve as an important tool to both increase the overall well-being of individuals suffering from stress and anxiety and to improve domains of cognitive function such as attention. Moreover, our web-based MMTs provide a larger portion of the population with a validated tool to improve their overall mental health and physical well-being.

As future directions, we plan to employ the current web-based mindfulness training in clinical populations, such as in obsessive–compulsive disorder (OCD) and ADHD patients, hoping to see similar effects predominantly on stress, anxiety, flow experience, and cognitive capacities. As well as to better understand the neurological mechanisms of action behind these changes, and how these can help in the treatment and prognosis of psychiatric diseases.

Data availability

The datasets generated during and/or analysed during the current study are available in the Open Science Framework (OSF) repository, https://doi.org/10.17605/OSF.IO/NAXC8.

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Author contributions

M.G.M.Á., B.B., B.K.H., M.W., and K.K. designed the study. M.G.M.Á., B.B., M.W., and E.H. recruited participants. M.G.M.Á., B.B., M.W., E.H., A.T., and E.E.T. acquired the data, which M.G.M.Á. analyzed. M.G.M.Á. also wrote the manuscript and prepared all figures and tables. All authors reviewed the manuscript. K.K. supervised the project.

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B.K.H. commercially provides access to the online mindfulness training that was used as the experimental treatment in this study. The other authors do not have competing interests.

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Localizing the human brain response to olfactory stimulation: A meta-analytic approach

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ABSTRACT

The human sense of smell and the ability to detect and distinguish odors allows for the extraction of valuable information from the environment, thereby driving human behavior. Not only can the sense of smell help to monitor the safety of inhaled air, but it can also help to evaluate the edibility of food. Therefore, in an effort to further our understanding of the human sense of smell, the aim of this meta-analysis was to provide the scientific community with activation probability maps of the functional anatomy of the olfactory system, in addition to separate activation maps for specific odor categories (pleasant, food, and aversive odors). The activation likelihood estimation (ALE) method was utilized to quantify all relevant and available data to perform a formal statistical analysis on the inter-study concordance of various odor categories. A total of 81 studies (108 contrasts, 1053 foci) fulfilled our inclusion criteria. Significant ALE peaks were observed in all odor categories in brain areas typically associated with the functional neuroanatomy of olfaction including the piriform cortex, amygdala, insula, and orbitofrontal cortex, amongst others. Additional contrast analyses indicate clear differences in neural activation patterns between odor categories.

1. Introduction

Neuroimaging methods have extensively been used to explore the functional neuroanatomy of olfaction; this is largely due to the fact that our ability to smell plays an essential role in our everyday lives by helping to extract valuable information from the environment, subsequently driving a behavioral response (Boesveldt et al., 2010; Sorokowska et al., 2017; Veldhuizen et al., 2010). While the chemosensory community has reached a general consensus on the primary and secondary olfactory cortices through various literature reviews (Sela and Sobel, 2010; Yeshurun and Sobel, 2010; Zelano and Sobel, 2005), in addition to initial meta-analyses conducted by Seubert et al. (2013) on all odors, Zou et al. (2016) on pleasant odors, and Huerta et al. (2014) on food odors, the research pertaining to human neuroimaging, olfaction, and its individual processing nodes for various odor categories continues to increase and its relevance continues to rise.

The current meta-analysis seeks to provide the scientific community with an updated perspective on the functional neuroanatomy of the olfactory cortex for the following reasons: 1) since the publication of Seubert et al. (2013), over 1,000 relevant articles pertaining to neuroimaging and olfaction have been published; the current meta-analysis is therefore effectively able to investigate more than double the total number of studies included in the initial meta-analyses. Additionally, the current meta-analysis seeks to 2) implement more robust meta-analytic methods (Eickhoff et al., 2012) and guidelines developed by Muller et al. (2018). Our research protocol was therefore prospectively registered to PROSPERO, an international database of systematic reviews (http://www.crd.york.ac.uk/PROSPERO/), while additionally utilizing the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) to report our data and results (Moher et al., 2009). The utilization of the guidelines is imperative due to the fact that the way in which a meta-analysis is conducted can strongly influence its

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conclusions (Nakagawa et al., 2017). And finally, not only does this meta-analysis contain detailed and relevant information on the functional neural anatomy of the human olfactory cortex, it also 3) provides an all-encompassing perspective on the individual processing nodes of the olfactory cortex for various odor categories. The current meta-analysis therefore effectively differentiates itself from the previously conducted research thus ultimately demonstrating the need to provide the scientific community with an up-to-date meta-analysis investigating the olfactory cortex.

The comprehensive nature of this meta-analysis additionally supports previous research which has demonstrated that, on the cerebral level, odors are grouped into distinct odor categories for positive and negative valence thus allowing for quick judgements and responses to be made (Boesveldt et al., 2010). In fact, the reaction time to the detection of negative or aversive odors (e.g. rancid, rotten, smokey, or bitter odors) has been observed to be faster than to positive odors, thereby allowing for a more rapid behavioral response to potentially harmful or dangerous stimuli in the environment (Boesveldt et al., 2010). Threatening odorous stimuli are therefore prioritized by the cerebral system to allow for a faster “fight or flight” response (Boesveldt et al., 2010; Iravani et al., 2021).

Not only does the ability to distinguish between positive and negative odors allow for the avoidance of hazardous situations, but our sense of smell additionally plays an important role in our eating behavior. In fact, the detection of food odors can initiate a series of physiological and biochemical responses to help prepare for the ingestion and digestion of food; these include the release of saliva, hormones, and digestive enzymes in various organs (Smeets et al., 2010). It has also been demonstrated that the presence of food odors can immediately elicit appetite-enhancing effects (Ramaekers et al., 2016) thereby suggesting that the human body also has a rapid response mechanism to encourage or motivate individuals to eat in the presence of food (Ramaekers et al., 2014). Given the essential role odors play in our everyday lives, this meta-analysis aims to provide the scientific community with a deeper understanding of the mechanisms underlying the neural responsivity to general olfaction and the individual processing nodes for various odor categories.

2. Methods

2.1. Meta-analytic process & protocol registration

Our research protocol was prospectively registered to the PROSPERO database (registration number: CRD42020157138) prior to the start of the meta-analytic process. While there were no deviations from the research protocol, two additional literature searches were conducted for aversive odors and pleasant odors, as reported in the following paragraphs.

2.2. Literature search strategy

To identify relevant literature pertaining to human olfaction and functional neuroimaging, a multi-step procedure was utilized.

The following terms were selected for the initial literature search in an effort to identify all relevant publications for overall odor processing: *functional magnetic resonance imaging OR fMRI OR cerebral blood flow OR positron emission tomography OR PET AND Olfact* OR Odor* OR Odour* OR smell* NOT Animal.* The asterisk (wild card) was used to capture all possible search term endings thereby allowing for the identification of all relevant publications in all odor categories. Three additional literature searches were subsequently conducted with the objective to identify publications pertaining to specific odor categories. These categories included: pleasant odors, food odors, and aversive odors. For each category-specific literature search, the key terms were adjusted accordingly (for the exact search terms used for all literature searches and search engines, please see the appendix). Literature searches were conducted via PubMed, Google Scholar, and SCOPUS to identify all relevant publications published prior to May 2020. A final literature search was conducted in April 2021 to ensure that no new and relevant publications were overlooked; the results and figures were adjusted accordingly.

The initial screening of all publications identified by the literature search results encompassed reading each publication’s title and abstract to ensure that human subjects were included, neuroimaging techniques (MRI or PET) were utilized, and that the olfactory cortex, or olfaction, was a part of the publication’s primary research question. If these criteria were evident in the title and abstract, the full publication was read (with a focus on the method’s section) to screen for the fulfillment of the following inclusion criteria.

2.3. Inclusion criteria

In an effort to determine whether a given publication and its corresponding dataset could be included in the meta-analysis, the following inclusion criteria were selected based upon the guidelines provided by Muller et al. (2018):

1) Whole-brain data needed to be reported; region of interest (ROI), volume of interest (VOI), or small volume corrected (SVC) results were excluded as were publications reporting correlations of BOLD signal change.
2) The stimulus used in the study needed to be exclusively odorous; studies during which additional or interacting stimuli such as tastants or trigeminal stimuli were presented were excluded, . This was done to ensure pure odor activations were observed and that activations caused by other sensory stimulation were not included.
3) Odorous stimuli needed to be presented to the participants orthonasally.
4) Odorous stimuli needed to be contrasted against an odorless baseline; direct contrasts of two odorous stimuli were excluded.
5) Only one contrast per odor category per study was included in the meta-analysis. An exception to this rule was made when a study reported the activations of males and females separately. In such instances, two contrasts from the same study per odor category were included; this was justified as the contrast represented different subject groups.
6) Only the contrasts of young, healthy, participants were included; contrasts based on patient or geriatric populations were excluded.
7) Contrasts were only included if they originated from samples of ≥ 10 participants.
8) Contrasts were included regardless of the task performed by the participants; this was justified as activations not mediated by olfactory processing would be identified as outliers by the ALE analysis. Additionally, the ALE generates outputs providing information on how much a particular study influenced the results. This information, allows for the observation of how much a study - and therefore also a particular task- influenced the activation probability maps.
9) The publication from which we extracted the contrast needed to provide sufficient information about the experimental and control tasks in an effort to be included in the meta-analysis.
10) All peak coordinates needed to be reported in the publication or supplementary materials in standardized stereotaxic space i.e., MNI (Montreal Neurological Institute) or Talairach.

If the publication fulfilled all the inclusion criteria, the following information was extracted: contrast-specific activation foci, stereotaxic space of reported foci, odor category, control for odor valence, task, experimental design, stimulus length, magnetic field strength of the MRI scanner, and the repetition time (TR) of the fMRI sequence.

Finally, to ensure that the extraction of the foci coordinates was not subject to human error, the list of coordinates was inspected and compared to the original articles a second time, in addition to a random check conducted by author KK.

2.4. Procedure and statistical calculations

The analyses were performed using an ALE algorithm developed by Simon Eickhoff on MATLAB (Eickhoff et al., 2009). The algorithm was originally developed by Turkeltaub et al. (2002) and was later modified by Eickhoff et al. (2009). When conducting a coordinate based meta-analysis, the overall objective of an ALE analysis is to quantify inter-study concordance of empirical neuroimaging studies (Turkeltaub et al., 2002). The x-, y-, and z-coordinates of peak activation (or foci) are entered into the algorithm across studies and are converted to the same standardized coordinate space. The foci are subsequently modeled as 3D Gaussian probability distributions centered at the given foci coordinate to account for the spatial uncertainty typically associated with neuroimaging data (i.e. the uncertainty accompanying spatial normalization or inter-subject anatomical variations, see Turkeltaub et al. (2002). The Gaussian widths are calculated based on the number of subjects represented in a given foci thereby weighing the foci based on the study's sample size, which ultimately allows for the effective assessment of the overlap between foci (Turkeltaub et al., 2002).

Individual maps of activation likelihood (MA maps) are calculated for each study by taking the voxel wise union of the Gaussians for all foci derived from that contrast (Turkeltaub et al., 2002). The subsequent permutation analyses of randomly generated sets of coordinates (as provided by the modified ALE algorithm by Eickhoff et al. (2009) calculates the voxel-wise union of MA maps across experiments, and allows for the ability to distinguish between truly converging foci across studies and noise to thus ultimately identify brain regions that show a consistent response across studies (Eickhoff et al., 2012; Turkeltaub et al., 2002). Resulting MA maps are corrected at $p < 0.05$ family-wise error (FWE) at the voxel level. This analysis allows for random-effects inferences which permit a generalization of the results to be made to the entire population of studies included in the analysis (Eickhoff et al., 2009, 2016). This analysis protocol was applied to all odor categories (all odors, pleasant odors, food odors, and aversive odors). Finally, the ALE algorithm generates a list of clusters which have sustained the statistical threshold in addition to providing the peak coordinate values within each significant brain region and the volume (mm^3) of each significant activation cluster.

Additional contrast analyses were performed using the ALE algorithm to identify the specific processing nodes for pleasant, food, and aversive odor categories. Contrast analyses were conducted using the same ALE algorithm provided by Eickhoff et al. (2011). When performing a contrast analysis, two sets of foci (which are loaded into the algorithm as individual contrasts) are examined for significant differences in convergence; to observe these differences, the individual contrasts are subtracted from each other. To account for potential differences between the studies included in the individual contrasts, the algorithm generates a null-distribution under the null-hypothesis of label exchangeability by randomly reassigning labels to the datasets (which is equivalent to randomly redistributing the studies into two groups) and computes the difference for the two datasets. Many permutations of this step are executed thereby ultimately yielding the null-distribution of the ALE difference which are then thresholded (Eickhoff et al., 2011).

The contrast analyses in this meta-analysis include category specific contrasts for food odors versus non-food odor stimuli, pleasant odors versus aversive odor stimuli, and food odors versus aversive odor stimuli. These contrasts were selected to identify the individual processing nodes for each odor category. While the contrasts food versus non-food odors, and pleasant versus aversive odors may seem like natural antitheses of each other, the contrast food versus aversive odors was selected to observe the activations of two odor categories which may have been essential to the evolutionary development of the human olfactory cortex. As olfaction is, from an evolutionary perspective, one of the oldest sensesory systems that enables organisms to find food and avoid predators (Hoover, 2010), we were interested in observing how the neural activation patterns of a food odor, which motivates an individual to approach and engage with the odorous stimulus differs from an aversive odor which may motivate the individual to flee from or avoid a potentially harmful odorous stimulus.

Additionally, the anatomical labels were provided by the Anatomy Toolbox v3.0 (Eickhoff et al., 2017) and the Atlas of the Human Brain (Mai et al., 2015). All anatomical labels per peak activation were reported (in decreasing likelihood) in the results section. The visualization of these results were constructed using a combination of the BrainNet-Viewer Toolbox (Xia et al., 2013) and Mango (RII, 2013).

3. Results

3.1. Literature search results

The extensive systematic literature search used to locate all relevant and available empirical data identified a total of 1895 publications (1170 for the initial literature search and 725 publications for the odor-specific literature searches). A depiction of the summary of the literature searches can be found in Fig. 1. Of these 1895 publications, 81 fulfilled all inclusion criteria of which 108 relevant contrasts could be extracted and provided 1053 foci. All 108 contrasts (1053 foci) were used in the all odor analysis, 38 contrasts (302 foci) for the pleasant odor analysis, 24 contrasts (232 foci) for the food odor analysis, and 18 contrasts (293 foci) for the aversive odor analysis. All foci coordinates, activation probability maps, in addition to the supplemental information extracted from each study will be available on ANIMA: a data-sharing initiative for neuro-imaging meta-analyses (https://anima.fz-juelich.de/) (Reid et al., 2016). Additionally, a list of all studies and contrasts included in this meta-analysis, as well as a table indicating whether a study controlled for perceived odor pleasantness and intensity can be found the supplementary section in Tables S1 and S2, respectively.

3.2. Significant ALE values for odor processing

The ALE for ‘all odors’ vs ‘baseline’ revealed the highest activation probability in the amygdala, piriform cortex, orbitofrontal cortex, as well as in the insula. As evident in Table 1 and Fig. 2a, the peaks in the fronto-temporal junction (incl. amygdala and piriform cortex) demonstrated bilateral activations and were larger than any other reported peak value. The highest activation probability was reported in a cluster of the left amygdala, which extended into the piriform cortex, parahippocampal gyrus, orbitofrontal cortex (OFC), and insula. The ALE also presented bilateral high-probability peak activations in the OFC, the insula, the parahippocampal gyrus, in addition to the left caudate.

3.3. Category-specific odor activations

We additionally assessed category-specific odor activations for pleasant odors, food odors, and aversive odors. To assess these activations, we conducted individual ALE analyses for each odor category within which we contrasted the odor-category against odorless air.

3.3.1. Pleasant odor analysis

The ALE for pleasant odors revealed the highest activation probability in the bilateral amygdala which extended into the piriform cortex. The larger activation cluster was, however, observed in the right hemisphere. The ALE analysis also presented high, bilateral probability peak activations in the OFC, in addition to the right insula, left pallidum, left putamen, and the central opercular cortex (see Table 1 and Fig. 2b).

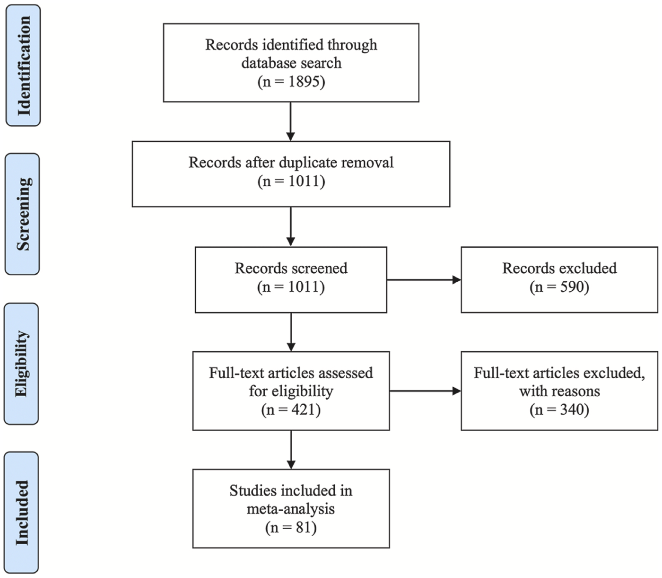

Fig. 1. provides a summary of the literature search process as provided by the PRISMA flow-chart.

3.3.2. Food odor analysis

The ALE analysis for food odors also revealed the highest bilateral activation probability in the amygdala which extended into the piriform cortex. The larger activation cluster presented in the left hemisphere. High-probability peak activations were also observed in the anterior division of the left parahippocampal gyrus and left entorhinal cortex (see Table 1 and Fig. 2c).

3.3.3. Aversive odor analysis

The ALE for aversive odors revealed unilateral activations in the right hemisphere with the highest activation probability in the right insula, right postcentral gyrus, and right amygdala. Bilateral activations did however become evident when, for exploratory purposes, a more liberal threshold (threshold free cluster enhancement $p < 0.05$) was applied (see Table 1 and Fig. 2d).

3.4. Effects of food odors: contrast analyses

Additional analyses were implemented with a specific focus on food odors in an effort to determine the individual processing nodes responsible for food odor perception and processing. To capture these processing nodes, contrast analyses were conducted in which food odor activations were contrasted against non-food odors activations. The *food > nonfood* analysis presented the strongest bilateral activation probabilities in the entorhinal cortex, amygdala, piriform cortex, and the parahippocampal gyrus with the larger activation in the left hemisphere. Additional activations were observed in the right insula as well as a bilateral putamen activation with the larger activation in the left hemisphere

The converse analysis *nonfood > food* presented the highest activation probabilities in the insula with the larger activation cluster in the left hemisphere. Additional activations in the left hemisphere were observed in the frontal operculum cortex, OFC, cingulate and paracingulate gyrus. In the right hemisphere, small activation clusters were additionally found in the amygdala, piriform cortex, putamen, and pallidum (For both contrasts see Table 2 and Fig. 3a).

In an effort to extract more information from food odors, we additionally contrasted food odors and aversive odors. The *food > aversive* contrast presented the highest activations in the left amygdala, piriform cortex, hippocampus, parahippocampal gyrus, temporal pole, entorhinal cortex, left pallidum and left putamen. While the converse analysis *aversive > food* presented the highest activations in the insula, and the OFC, in addition to the precentral gyrus, middle frontal gyrus, and postcentral gyrus (For both contrasts see Table 2 and Fig. 3b).

3.4.1. Pleasant vs aversive odors: contrast analyses

Contrast analyses were also conducted in an effort to observe the individual processing nodes for pleasant odors and aversive odors. To capture the unique activations for pleasant odors versus aversive odors, the contrast *pleasant > aversive* was conducted. Results demonstrated greater activations in the left hippocampus, amygdala, parahippocampal gyrus, OFC, and temporal pole. The converse analysis, *aversive > pleasant*, presented results with activation clusters in the insula, amygdala, hippocampus, frontal occipital cortex, temporal pole, frontal operculum, and the cingulate gyrus (For both contrasts see Table 2 and Fig. 3c).

As previously stated, all foci coordinates in addition to the activation probability maps and the supplemental information extracted from each study will be available on ANIMA: a data-sharing initiative for neuroimaging meta-analyses (https://anima.fz-juelich.de/) (Reid et al., 2016).

4. Discussion

As olfaction is considered to be one of the oldest sensesory systems that enables organisms to find food, mates, and avoid predators (Hoover, 2010), this study was designed in an effort to achieve two main aims: our first aim was to use a meta-analytic approach to quantify inter-study concordance to ultimately generate activation probability maps for the functional neuroanatomy of the olfactory cortex. Our second aim was to determine the individual processing nodes for different odor categories through the implementation of separate ALE analyses and contrast analyses. We observed strong, reliable activations in cortical structures previously identified as the primary and secondary olfactory cortices.

Table 1
Peak Activation Probabilities for All Odors, Pleasant Odors, Food Odors, and Aversive Odors.

Category:	Cluster	Anatomical Label	k	Coordinates			Z
				x	y	z	
All Odor	1	L. Amygdala L. Piriform cortex L. Parahippocampal gyrus, anterior division	1163	−22	0	−20	0.127
		L. OFC (posterior orbital gyrus) L. Frontal pole		−26	32	−12	0.0635
		L. Insula		−40	6	−10	0.0545
		L. Insula (frontal operculum) L. OFC		−34	22	−2	0.0448
	2	R. Amygdala R. Piriform cortex R. Parahipppocampal gyrus, anterior division	886	24	4	−18	0.0108
		R. Insula		38	6	−12	0.0505
	3	R. OFC (posterior orbital gyrus) R. Frontal pole	34	24	32	−16	0.0416
	4	L. Caudate	9	−12	8	2	0.0424
	5	R. Insula (frontal operculum) R. Central opercular cortex	8	36	−6	12	0.0382
	6	Paracingulate gyrus Cingulate gyrus, anterior division	4	0	22	40	0.0353
Pleasant Odor	1	R. Amygdala R. Piriform cortex R. Parahippocampal gyrus, anterior division R. Piriform cortex	247	26	2	−18	0.0564
	2	L. Amygdala L. Piriform cortex	213	−22	−2	−22	0.0566
	3	L. OFC (posterior orbital gyrus) L. Frontal pole	11	−26	32	−12	0.0251
	4	L. Insula L. Central opercular cortex	8	−42	8	0	0.0247
	5	L. Pallidum L. Putamen	2	−16	8	0	0.0242
Food Odor	1	L. Amygdala L. Piriform cortex L. Parahipppocampal gyrus, anterior division L. Entorhinal cortex	228	−20	0	−20	0.0407
	2	R. Amygdala	67	28	0	−20	0.0235
		R. Amygdala R. Piriform cortex		28	0	−14	0.0222
Aversive Odor	1	R. Insula	43	40	6	−10	0.0321
	2	R. Precentral gyrus	4	42	−12	38	0.0236
	3	R. Amygdala	3	20	−2	−16	0.0222

These structures include the piriform cortex which is a brain area that receives direct input from the olfactory bulb and other brain areas receiving indirect input from the olfactory bulb such as the amygdala, insula, and the OFC (Carmichael et al., 1994; Firestein, 2001; Shipley and Reyes, 1991). Additional cortical and subcortical structures were identified within our analyses which could be attributed to the olfactory processing of odor identification, valence, and intensity judgements. Within the following paragraphs, we will delve into the activations observed in the analyses and describe how they may functionally contribute to olfactory processing.

4.1. *Piriform cortex and amygdala activation*

Within this meta-analysis we observed robust activations in the piriform cortex and the amygdala (with the exception that no piriform activation was observed in the aversive odor analyses). These results emphasize the fundamental role the piriform cortex and amygdala have in olfactory processing. While the piriform cortex not only contributes to the distribution of odor information, it is also said to (second to the olfactory bulb) play a prominent role in the extraction of relevant odor information to facilitate odor recognition (Blazing and Franks, 2020; Rolls et al., 2003; Russo et al., 2020). The amygdala, in turn, through its connection with the piriform cortex, has been argued to be involved in the evaluation of emotional qualities in detected odors (i.e., its salience, intensity, valence, and arousal), thereby contributing to hedonic processing and allowing for quick, positive or negative judgements to be made (Winston, 2005). An observed activation in the amygdala during the presentation of odorous stimuli is, for this reason, critical in helping to prepare for the appropriate behavioral response (Soudry et al., 2011) and is essential for all odor categories.

Pleasant Odors: Our robust activations observed in the piriform cortex and amygdala for pleasant odor stimuli corroborate several studies reporting similar activation patterns in the presence of pleasant odors (Kjelvik et al., 2012; Lombion et al., 2009; Soudry et al., 2011). In fact, positive correlations between amygdala activation and the perceived pleasantness of an odor have previously been observed (De Araujo et al., 2005).

Food Odors: In addition, activations in the amygdala and piriform cortex were observed for food odor stimuli. As the presence of food odors can initiate the release of hormones and digestive enzymes which, in turn, motivates an individual to eat (Smeets et al., 2010), our observed activations may be explained by the fact that food odors are highly emotional and salient stimuli. Previous research demonstrated a positive correlation between the processing of emotionally salient stimuli, positive emotional memories, and the activation of the amygdala (García-García et al., 2020; Morris and Dolan, 2001; Winston, 2005).

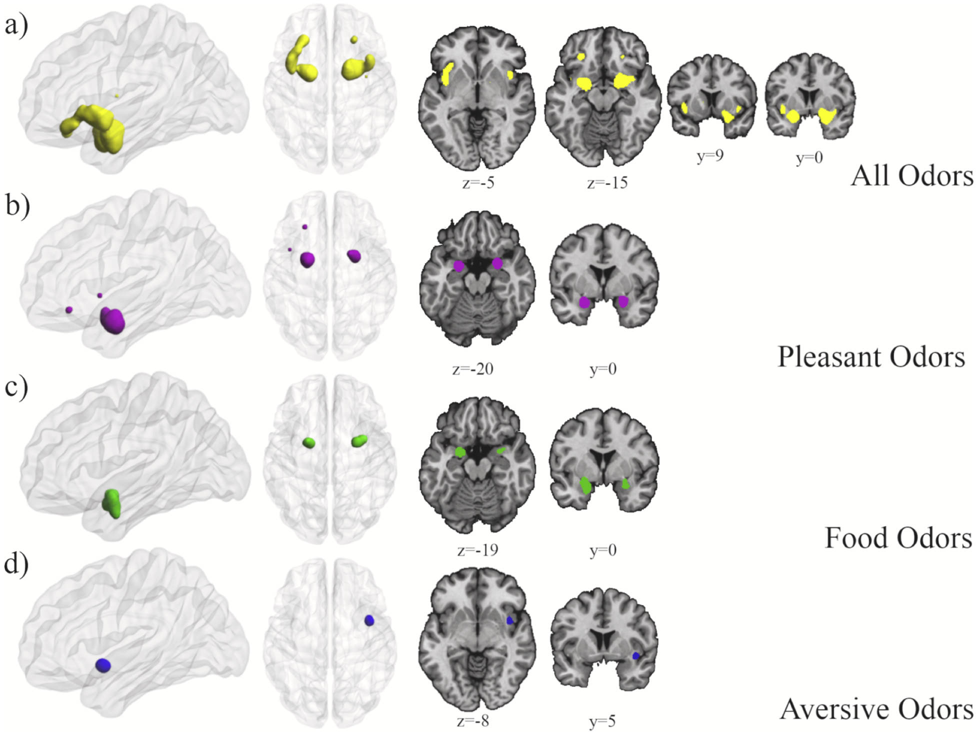

Fig. 2. Significant ALE activations for all odors, pleasant odors, food odors, and aversive odors contrasted against baseline. An MNI, standard anatomical brain template in neurological convention was used to overlay the significant activations for visualization purposes.

Another factor to consider is that the ingestion of inedible food could be harmful or even deadly. Therefore, the amygdala's ability, in conjunction with the piriform cortex, to quickly assign a positive or negative valence to food stimuli is essential to our eating behavior.

Aversive Odors: Again, the ability to identify aversive or disgusting odors is essential for survival. The observed amygdala activation for aversive odors becomes even more striking when we consider the finding that the medial amygdala evolved from the olfactory system (Schoenbaum et al., 2009); From an evolutionary standpoint, this presumably occurred in an effort to extend the ability to detect threats from odors in the environment (Schoenbaum et al., 2009). The amygdala not only contributes to the evaluation of an odorous stimulus as being positive or negative, but also plays a crucial role in threat-detection, ultimately helping to prepare a quick fight or flight response (Soudry et al., 2011). Interestingly, the fact that we did not observe activations in the piriform cortex in the aversive odor analyses is supported by a recent electroencephalography (also known as EEG) study in which it was observed that negative odors elicited a response in the olfactory bulb while it was only minimally activated in response to pleasant odors (Iravani et al., 2021). Our lack of piriform cortex activation could therefore indicate that the processing of negative odors occurs very early in the olfactory system due to the need to make quick judgements about harmful stimuli in the environment. Our consistent and robust activations in the amygdala and lack of piriform cortex activation demonstrates the vital role of quick olfactory processing in the presence of negative odors.

4.2. Orbitofrontal cortex (OFC) and insula activations

The OFC and the insula are known to play a unique role in olfactory processing as they receive projections from the piriform cortex and the amygdala, thereby also receiving indirect projections from the olfactory bulb and tract (Albrecht et al., 2009; Patin and Pause, 2015; Soudry et al., 2011). The OFC and the insula are therefore known for their role to integrate olfactory and other multimodal information from the environment (Gottfried and Dolan, 2003; Vaughan and Jackson, 2014), in addition to being involved in higher-order odor processing such as the continuing assessment of an odor's affective value (Rolls, 2019; Seubert et al., 2010; Wicker et al., 2003a). While activations in the insula have been attributed to the fundamental processing of valence or emotion, the OFC is considered to additionally play an active role in odor identification, reward value, and affective learning (Rolls, 2019; Soudry et al., 2011).

Pleasant Odors: Our observed OFC and insula activations in the pleasant odor analyses support the previous findings demonstrating the OFC and insula's crucial role in processing pleasant and emotional odors (Rolls, 2019; Soudry et al., 2011).

Food Odors: While we did not observe an activation in the OFC, our observed activation in the insula in the food odor analyses could be justified due to the multisensory nature of food stimuli (Lundström et al., 2011). During the consumption of food, all senses are engaged; not only are we smelling the food, tasting its different flavors, touching the food or feeling its different textures in our mouths, but we are also simultaneously seeing the food, and even extracting information about the food through sound. The insula, in turn, has been demonstrated to play an

Table 2
Peak Activation Likelihood for Contrast Analyses.

Analysis:	Cluster	Anatomical Label	k	Coordinates			T
				x	y	z	
Food > Nonfood	1	L. Entorhinal cortex L. Amygdala L. Parahippocampal gyrus, anterior division	118	−16	−2	−32	2.66
	2	R. Entorhinal cortex R. Amygdala R. Parahippocampal gyrus, anterior division	35	18	−2	−30	2.69
	3	R. Planum polare R. Insula	24	38	0	−22	2.17
	4	R. Putamen	17	30	2	−8	2.17
	5	L. Amygdala L. Piriform cortex	7	−22	2	−14	1.79
	6	L. Putamen L. Pallidum	1	−20	−2	−4	1.72
NonFood > Food	1	L. Insula	313	−34	2	−2	3.22
		L. Insula L. Frontal operculum cortex		−40	4	4	2.9
		L. Insula L. Frontal operculum cortex		−34	10	8	2.74
		L. Frontal operculum cortex L. Central operculum cortex		−40	10	10	2.73
		L. Inferior frontal gyrus L. Frontal operculum cortex L. Insula		−36	20	20	2.14
	2	R. Insula R. OFC	187	36	14	−10	2.53
		R. Claustrum R. Insula R. OFC		28	24	−2	1.95
		R. Insula R. OFC		32	26	−2	1.9
	3	L. Frontal pole L. OFC	157	−32	38	−14	2.59
	4	R. Cingulate gyrus, anterior division	87	4	16	38	2.17
		R. Paracingulate gyrus R. Superior frontal gyrus		2	22	44	2.07
		R. Paracingulate gyrus R. Superior frontal gyrus		2	28	46	1.98
		R. Cingulate gyrus, anterior division R. Paracingulate gyrus		0	12	40	1.98
		R. Cingulate gyrus, anterior division R. Paracingulate gyrus		4	12	38	1.94
	5	R. OFC R. Amygdala R. Piriform cortex	58	24	8	−18	2.2
	6	R. Substantia nigra	13	−12	−14	−12	1.89
	7	R. Putamen R. Pallidum	1	16	8	−4	1.67
	8	L. OFC	1	−38	28	−2	1.65
	9	L. Frontal operculum cortex L. Central opercular cortex	1	−40	26	0	1.7
Food > Aversive	1	L. Parahippocampal gyrus L. Amygdala L. Entorhinal cortex	222	−14	−2	−26	2.75
		L. Amygdala L. Hippocampus		−24	−8	−20	2.13
		L. Amygdala L. Parahippocampal gyrus		−28	−2	−16	2.04
		L. Amygdala L. Temporal pole		−30	2	−18	1.97
	2	R. Entorhinal cortex R. Amygdala R. Parahippocampal gyrus	178	20	4	−3	267
		R. Amygdala R. Entorhinal cortex		32	−2	−18	2.32
		R. Temporal pole R. Amygdala R. Entorhinal cortex R. Parahippocampal gyrus		28	8	−26	2.14
	3	L. Putamen L. Pallidum L. Piriform cortex	3	−22	2	−6	1.82

(*continued on next page*)

Table 2 (*continued*)

Analysis:	Cluster	Anatomical Label	k	Coordinates			T
				x	y	z	
Aversive > Food	1	R. Insula R. Temporal pole	263	38	12	−8	3.41
		R. Insula R. OFC		36	20	−8	2.91
		R. OFC R. Insula		34	24	−4	2.34
	2	R. Precentral gyrus R. Postcentral gyrus	99	40	−12	34	2.61
		R. Precentral gyrus R. Middle frontal gyrus	42	−8	44	2.5	
		R. Postcentral gyrus R. Precentral gyrus	40	−16	34	2.49	
		R. Precentral gyrus R. Postcentral gyrus	44	−10	36	2.46	
		R. Precentral gyrus R. Postcentral gyrus	42	−12	42	2.3	
Pleasant > Aversive	1	L. Hippocampus L. Parahippocampal gyrus, anterior division L. OFC L. Temporal pole	158	−20	−8	−22	2.15
	2	R. Amygdala R. Temporal pole R. Parahippocampal gyrus	108	28	8	−26	2.27
Aversive > Pleasant	1	R. Insula R. OFC	525	36	20	−8	3.67
		R. Planum polare		42	0	8	3.22
		R. Temporal pole		44	4	−14	3.19
		R. Frontal operculum cortex		48	20	0	2.59
	2	L. Amygdala L. Hippocampus L. Anterior olfactory nucleus	17	−14	12	−14	2.25
	3	L. Insula	14	−36	−2	2	1.95
	4	L. Paracingulate gyrus	13	−2	28	34	1.86
	5	R. Amygdala	12	20	−4	−16	1.84
	6	L. OFC	12	−40	26	−14	1.88
	7	R. Superior frontal gyrus	12	6	28	46	2.05
	8	R. Cingulate gyrus	11	4	22	30	2.19
	9	R. Insula	3	38	−10	14	1.77
	10	L. Frontal operculum cortex	2	−42	10	10	1.82
	11	L. Temporal pole	1	−46	10	−12	1.71
	12	L. OFC	1	−44	22	−6	1.65
	13	R. Insula	1	34	0	8	1.7

active role in the integration of these multi-sensory, aspects of emotion and interoceptive awareness, while also playing a major role in the neural control of appetite and the regulation of energy balance (Frank et al., 2013). The insula, in relation to the consumption of food, is therefore involved with the processing of external sensory information and has even been linked to reward processing thereby helping to contribute to the hedonic processing system (Berthoud and Munzberg, 2011).

Aversive Odors: Similarly, within the aversive odor analyses we only observed a robust insula activation without observing an OFC activation. This robust insula activation could be due to the fact that the insula has been demonstrated to be essential in threat detection given its direct connection to the amygdala, thereby allowing for quick behavioral responses to a potentially threatening (or aversive) odorous stimulus in the environment to be made (Wicker et al., 2003b).

4.3. Paralimbic activations

Many of the paralimbic structure activations observed in our results support the emotional quality of olfactory stimuli while also indicating the presence of a network of structures involved in the processing of memory and emotion during olfaction. These brain areas include the parahippocampal gyrus, entorhinal cortex, hippocampus, paracingulate gyrus, precentral gyrus, caudate nucleus, frontal pole, putamen, pallidum, and the central opercular cortex. Although some of these brain areas are not classically associated with olfactory processing, areas could be linked to the emotional or memory processing of olfactory stimuli. While previous research demonstrated the parahippocampal gyrus' ability to provide extensive cortical input to the entorhinal cortex (Olofsson et al., 2013), the entorhinal cortex, in turn, is the source of the major efferent projections to the hippocampus. These brain areas are therefore said to play a key role in memory encoding and retrieval which is an important factor in odor identification (Ward et al., 2014). Previously encountered odors and their memory associations could allow for more efficient odor identification and the subsequent behavioral response to those odors. While we observed activations in the parahippocampal gyrus for the all odor, pleasant odor, and food odor analyses, we interestingly only observed activations in the entorhinal cortex in the food odor analyses. This could potentially be explained by the fact that food odors, as previously mentioned, are very emotionally salient and allow for positive or negative associations with food to be quickly recalled. The ability to rapidly recall these salient, emotional food stimuli could be essential to an individual's health and survival.

An additional activation found in the frontal pole in our all odor and pleasant odor analyses may be critical for integrating the olfactory and semantic networks (Olofsson et al., 2013) while also aiding in the processing of future reward (Okuda et al., 2003). The pallidum and putamen activations also found in the pleasant odor ALE are supported by

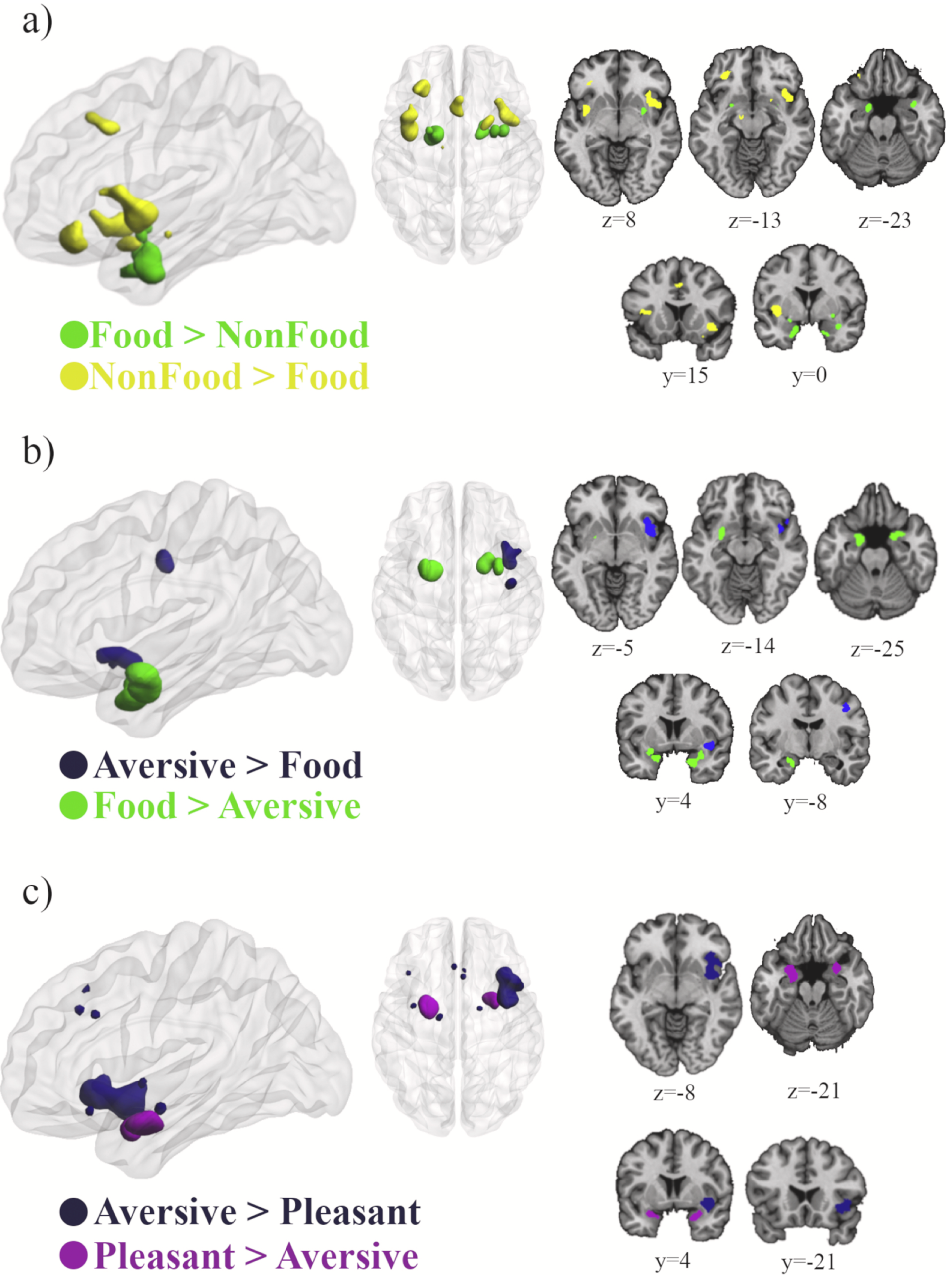

Fig. 3. a-c. A visualization of the significant activations observed in the contrast analyses conducted. An MNI, standard anatomical brain template in neurological convention was used to overlay the significant activations for visualization purposes.

previous research in which these brain areas were both deemed to be likely candidates to mediate the sensory experience of exposure to pleasantness and the limbic reward circuits (Haruno and Kawato, 2006; Tindell et al., 2006). Activations in the pallidum and putamen could not only indicate pleasant or hedonic encoding, but could also be an indicator for stimulus-action-reward associations (Haruno and Kawato, 2006; Tindell et al., 2006). Similarly, the observed activation in the caudate nucleus in the all odor ALE has not only been previously demonstrated to be associated with the learning and encoding of emotional stimuli, it has also been associated with the initiation of goal directed action, which is often necessary upon detecting a rewarding odor in the environment (Grahn et al., 2008). Similarly, in the aversive odor analyses, we observed a significant activation in the precentral gyrus, which is a part of the primary motor cortex. This activation could be associated with the preparation to initiate a fight or flight response in an effort to retreat from the potentially harmful odorous stimulus. In fact, the reaction time to the detection of negative odors (e.g. rancid/-rotten food) is faster than to positive odors thereby allowing for a quicker response to potentially harmful or dangerous stimuli in our environment (Boesveldt et al., 2010). Finally, the opercular cortex activation observed in the pleasant odor analyses has previously been associated with gustatory responses to pleasant stimuli (i.e. tastants) (Veldhuizen et al., 2010), and has also demonstrated to be functionally connected to the piriform cortex (Ruser et al., 2021) which may indicate its role in helping to initiate a response to said stimuli.

4.4. Clinical relevance

Previous research suggests that the reduction in the ability to smell can be an important preclinical indicator for various neurodegenerative diseases such as Alzheimer's disease (Djordjevic et al., 2008; Mesholam et al., 1998), Parkinson's disease (Doty et al., 1988), and Huntington's disease (Barrios et al., 2007). In addition, within the age of the SARS-CoV-2 pandemic in which, hyposomnia or anosmia (i.e., the reduction or loss of smell, respectively) have been identified as prominent symptoms of the disease (Hopkins et al., 2020; Lechien et al., 2020), understanding the neurobiological underpinnings of healthy olfactory processing could indirectly aid our understanding of olfactory dysfunction thereby providing insight on an important prognostic indicator for various neurodegenerative diseases and COVID-19.

4.5. Limitations

While the activation likelihood estimation (ALE) model is a powerful method to quantify inter-study concordance, the method does come with some inherent limitations. One of the primary limitations in conducting a meta-analysis is the inability to control for methodological differences between studies. While many of the methodological details of each study were extracted from each publication to be included in the ALE, it is simply not possible to control for all differences between the studies included in the meta-analysis. However, as previously stated, the result generated by the ALE was used to observe whether an individual study had a significant influence on the outcome of the ALE analysis; we are however, of course, not able to control for all possible influences. On a similar note, the studies included in the analysis have a publication date range from 1992 to 2019; significant technological and methodological advances made during this time-period may have additionally led to differences in reported activations. However, since the majority of the publications included in this meta-analysis were published over the past 10–15 years, we believe that the possible differences between older and newer publications should not have influenced the overall analysis results of the ALE.

5. Conclusion

With the completion of this meta-analysis, we were successfully able to contribute to the neuroimaging and chemosensory scientific communities by providing probability activation maps of the human olfactory cortex and its individual processing nodes for specific odor categories. With this information, we hope to be able to provide many disciplines with further insight into the processing of odors on the neuronal level.

Data availability

All foci coordinates, activation probability maps, in addition to the supplemental information will be available on ANIMA: a data-sharing initiative for neuro-imaging meta-analyses: anima.fz-juelich.de.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.neubiorev.2021.12.035.

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Manuscript: Project 3 | The Effectiveness of a Food-Related MMT

Mindfulness Training Reduces Mindless Eating Behavior: The effects of a food-related mindfulness training on stress-eating and brain function.

Abstract:

Background: Stress-related overeating can lead to excessive weight gain, increasing the risk of developing metabolic and cardiovascular disease. Mindfulness meditation training (MMT) has been demonstrated to reduce stress as well as increase interoceptive awareness. *Methods:* To investigate the effects of MMT on eating behavior, stressed, meditation-naïve, individuals (*N* = 66) were recruited to participate in either a 31-day, web-based, MMT or health training (HT) condition. Behavioral as well as resting-state MRI data were acquired. *Results*: The MMT, in comparison to the HT, was found to significantly reduce stress- and emotional-eating tendencies as well as food cravings, while also increasing perceived mindfulness. These behavioral results were corroborated through observed seed-based functional connectivity (FC) changes on the neuronal level: A-priori-selected seed regions fundamental in the regulation of eating behavior (i.e., the hypothalamus and insula) and the whole brain revealed MMT-related FC changes associated with the hypothalamus, reward regions, as well as several areas of the DMN in addition to observing FC changes between the insula and somatosensory areas. Further FC changes between seed regions and brain areas attributed to emotion regulation, awareness, attention, and sensory integration were also observed. Notably, FC changes significantly correlated with behavioral measures, thereby providing insight into the underlying neuronal mechanisms of MMT's effects on stress-eating.

This study is listed as a clinical trial on the ISRCTN registry with trial ID ISRCTN12901054

Introduction

Prolonged exposure to stress (i.e., chronic stress) has been demonstrated to have negative implications on many health-related domains including eating behavior. This is due in part to the nature of the physiological stress response which is comprised of the autonomic nervous system including the sympathetic and parasympathetic nervous systems in addition to the hypothalamic-pituitary-adrenal (HPA) axis (McEwen, 2007; McEwen & Stellar, 1993). While these systems, and their accompanying neuroendocrine pathways, work together to allow the body to effectively respond to acute stress (i.e., threatening stimuli in the environment), chronic stress can have negative consequences on physiological circuits (McEwen, 2007). For example, chronic stress can lead to the dysregulation of the HPA axis, which can result in the aberrant production of stress hormones such as cortisol (McEwen, 2007; McEwen, 2008). The excess secretion of cortisol elicits a series of cascading, negative, effects on the production of leptin, ghrelin, and neuropeptide Y, which all play an integral role in regulating perceived hunger and satiety, while also affecting metabolism as well as the storage of visceral fat tissue (Bose et al., 2009; Holmes et al., 2010; Kuo et al., 2007; McEwen, 2007; McEwen & Stellar, 1993; Sojcher et al., 2012). Chronic stress, and the subsequent dysregulation of the HPA axis, can, thereby, induce increased feelings of hunger, increased caloric intake, and weight gain (Adam & Epel, 2007; Epel et al., 2001; Groesz et al., 2012; Oliver et al., 2000; Torres & Nowson, 2007). In fact, prior research demonstrates that stressed individuals are more susceptible to selecting high-calorie foods, i.e., foods with a high fat, salt, or sugar content than non-stressed individuals (Oliver et al., 2000).

Furthermore, chronic stress has been shown to implicate emotion regulation and cognitive control (Mathews & MacLeod, 2005). This is particularly noteworthy as a large portion of the global population lives in an obesogenic environment, i.e., individuals are persistently being exposed to high-calorie food items (Hawkes, 2006; Lake & Townshend, 2006; Swinburn et al., 2011). Given that the mere presence of high-calorie food and its odors can elicit appetite-enhancing effects (Yeomans, 2006), stressed individuals may not only be more prone to experiencing an increase in appetite through the dysregulation of their HPA axis but may also be less able to utilize cognitive control (i.e., restraint) when encountering high-calorie foods.

Ultimately, the long-term effects of chronic stress and its influence on eating behavior can have negative implications on metabolic and cardiovascular health. For example, frequently engaging in stress-related overeating behavior (and the subsequent weight gain) can lead to type 2 diabetes, hypertension, and cardiovascular disease (Bray, 2004; Epel et al., 2000; Gami et al., 2007; Torres & Nowson, 2007). Given the profound effect stress has on eating behavior, its long-term health consequences, in addition to the high, global, prevalence of cardiovascular and metabolic disease (Benjamin et al., 2019; Hales et al., 2020; Virani et al., 2020), it is crucial for the scientific community to establish and investigate interventions that could reduce stress-related overeating behavior.

To this end, mindfulness meditation training (MMT) has been demonstrated to be a reliable stress-reduction mechanism that can also improve overall well-being (Creswell et al., 2014; Goyal et al., 2014; Hariprasad et al., 2013; Hölzel et al., 2011; Luders et al., 2013; Pickut et al., 2013; Sharma & Rush, 2014). Mindfulness meditation involves the intentional focus of attention as well as open awareness of the present moment without judgment or distraction (Kabat-Zinn, 2003a). Through its ability to bring attention to thoughts, feelings, and bodily sensations, MMT can support individuals in developing greater interoceptive awareness, emotion regulation, and reduce stress sensitivity (Butzer et al., 2015; Chong et al., 2011; D'Silva et al., 2012; Gard et al., 2014; Goyal et al., 2014; Lemay et al., 2019; Wahbeh et al., 2008). By becoming more aware of thoughts and emotions, individuals can observe stressors with greater objectivity and compassion, thereby reducing the physiological stress response in addition to the susceptibility to chronic stress (Creswell & Lindsay, 2014; Marcus et al., 2003; Miller et al., 2021). Given the role MMT plays in reducing perceived stress as well as the physiological stress response, it is hypothesized that individuals suffering from stress-related overeating behavior would benefit from a food-related MMT. In addition, while conventional dieting methods leave little room to follow natural hunger cues, MMT enables practitioners to become more aware of both their mind and body and allows for an increase in the perception of satiety and hunger, as well as stress and emotion cues. MMT could thereby alter the reactivity to food stimuli thus ultimately helping individuals lead a healthier lifestyle. The training utilized in the present study provides stress-eaters with an alternative to conventional, rigorous, diet plans that typically enforce calorie restriction, which is a method that only perpetuates the inability to listen to internal hunger cues.

As both stress and mindfulness have an effect on the neuronal level (Bremer et al., 2022; Brewer et al., 2011; Hölzel et al., 2011; Kilpatrick et al., 2011; Syan et al., 2021; Tang et al., 2015), this study seeks to investigate the effects of a food-related MMT on the behavioral as well as neuronal levels. To this end, participants underwent resting-state functional magnetic resonance imaging (rsfMRI), which is a neuroimaging method that provides insight into the underlying functional organization of the brain during rest. While an increase in functional connectivity (FC) between brain regions can imply stronger coupling (i.e., the degree to which the neural activity of one region is related to the neural activity of another region), a decrease in functional connectivity can imply a decoupling of the dependence between brain areas. Observed alterations in FC will, therefore, provide insight into the neural processes underlying the mechanisms through which MMT influences stress-eating behavior. While previous studies were able to successfully demonstrate

MMT-induced neuroplastic changes on resting state FC (Bremer et al., 2022; Creswell et al., 2016; Sezer et al., 2022; Taren et al., 2015; Taren et al., 2017), these studies utilized general MMT interventions. The aim of the present study, however, was to investigate meditation's specific influence on eating behavior through the application a food-specific MMT.

The hypothalamus and insula were, therefore, selected as regions of interest given their fundamental role in mediating the neural processes of perceived hunger and satiety cues. The hypothalamus, for example, when considering the role chronic stress plays in the dysregulation of the HPA axis, can initiate alterations in appetite and food intake, (Bose et al., 2009; Holmes et al., 2010; Kuo et al., 2007; McEwen & Stellar, 1993; Sojcher et al., 2012). While the hypothalamus, as a whole, helps to regulate both stress and eating behavior, the hypothalamus can be parcellated into two nuclei that each play a unique role in processing perceived hunger and satiety, i.e., the lateral hypothalamus and the medial hypothalamus, respectively. While the lateral hypothalamus is critical in initiating eating behavior through its ability to regulate hormones such as neuropeptide Y and agouti-related peptides, which stimulate eating behavior by increasing feelings of hunger (Aston-Jones et al., 2009; Bernardis & Bellinger, 1996; Saper et al., 2002; Syan et al., 2021), the medial hypothalamus, on the other hand, has been demonstrated to be involved in regulating perceived satiety, or feelings of fullness, through the release of hormones such as melanin-concentrating-hormone (MCH) (Saper et al., 2002).

Furthermore, a review published by Syan et al. (2021) was able to demonstrate differences in FC between individuals with obesity and controls in the medial and lateral hypothalami. Researchers demonstrated an increase in FC between the medial hypothalamus (responsible for eliciting satiety cues) and areas of the reward system suggesting an increased interdependence between perceived reward and perceived satiety in individuals with obesity. The review additionally demonstrated that, in comparison to controls, individuals with obesity exhibited an increase in FC between the lateral hypothalamus (responsible for regulating feelings of hunger) and somatosensory areas, indicating that individuals with obesity may be more sensitive to both the perception of hunger as well as the sensations of food in comparison to controls. These findings indicate that differences in eating behavior are accompanied by specific FC changes in the brain. Therefore, given its complex interplay between stress, appetite, and eating behavior, the hypothalamus was selected as a region of interest to allow for the observation of possible neuronal changes elicited by a food-related MMT.

Not only does the hypothalamus play an integral role in the processing of stress and eating behavior but the insula is a brain area that also contributes to cognitive processes underlying mindfulness meditation and eating behavior. For example, the insula has been demonstrated to be involved in interoception (i.e., perception of bodily sensations) and attentional control, which are both fundamental aspects of mindfulness meditation as well as eating behavior (Craig, 2009). Moreover, the insula has been demonstrated to play a role in the subjective experience of flavor, texture, and smell (Rolls & McCabe, 2007; Small, 2010; Torske et al., 2022), which are all factors that contribute to assessing the hedonic value of food. The insula, therefore, plays an integral role in eating behavior. Similar to the hypothalamus, the insula can be parcellated into individual nuclei allowing for closer inspection of its unique roles pertaining to the processing of mindfulness, stress, and eating behavior. For example, the insula can be parcellated into the anterior and posterior nuclei. Mindfulness meditation and its involvement in fostering awareness in addition to the acceptance of present-moment experiences has previously been associated with the anterior insula, an area of the brain involved in emotion regulation and interoceptive awareness (Farb et al., 2012; Hölzel et al., 2007; Laneri et al., 2017). Both emotion regulation and interoceptive awareness are particularly relevant to eating behavior as they help individuals tune into hunger and fullness cues, allowing for more mindful – or less emotion-dependent - food selections (Craig, 2009; Critchley et al., 2004).

The posterior insula, on the other hand, has been associated with sensory processing and the integration of taste-related stimuli (Rolls, 2006). Therefore, while the anterior insula may be responsible for regulating emotion regulation and interoceptive awareness, the posterior insula is involved sensory integration of food-related stimuli, which both ultimately influence food choice. Additionally, both the anterior and posterior insula have been demonstrated to integrate information signaling produced by the hormones ghrelin and leptin, as well as be involved in the processing of somatosensory information (Wright et al., 2016). The insula is, therefore, not only a brain area that is associated with regulating perceived hunger and satiety cues but also plays a fundamental role in mediating cognitive, emotional, and sensory processes related to both mindfulness and stress-related eating behavior. The insula and its individual nuclei, thus, serve as essential seed regions to observe FC changes to provide insight into the intersecting neural mechanisms of mindfulness meditation and eating behavior.

This research will not only allow for an improved understanding on how mindfulness training impacts stress-related overeating behavior, but it will also provide further insights into the neural mechanisms of eating behavior and stress reduction. The results of this study could additionally provide critical evidence of an effective intervention strategy for stress-eaters to improve overall well-being in addition to cultivating a more mindful relationship with food. If MMT serves to be an effective intervention strategy for stress-eating tendencies, the longer-term benefits of a food-related MMT could ultimately help to reduce the risk for developing cardiovascular and metabolic diseases.

Methods

Participants

In an effort to recruit individuals with the tendency to overeat when stressed, the present study was advertised via the university hospital's mailing list and online advertisements. Interested participants were required to report moderate to high levels of stress, as assessed by the perceived stress scale (PSS) (Cohen et al., 1983), and were considered eligible when meeting the following criteria: (1) between the ages of 18 and 45 (2) general MRI suitability (i.e., no metal implants and not prone to claustrophobia), (3) body-mass-index (BMI) between 18 and 30, (4) no dietary restrictions (including vegetarianism or veganism) (Bontempi et al., 2022), (5) no use of oral contraceptives or intrauterine devices, (6) no known, untreated, thyroid dysfunction, (7) no chronic respiratory diseases. All participants provided written, informed, consent and were given monetary compensation for their participation. this study is listed as a clinical trial on the ISRCTN registry with trial ID ISRCTN12901054 and was approved by the Ethics Committee of Klinikum Rechts der Isar, Technical University Munich. All methods were carried out in accordance with relevant guidelines and regulations.

Procedure

This study was designed as a pseudo-randomized, active control trial to investigate the effects of mindfulness meditation on stress-related overeating behavior and its neuronal correlates. All subjects enrolled were single-blindedly (subject only) allocated to one of two, equisized, groups to complete either the MMT condition or the active control, health training (HT), condition. All participants underwent magnetic resonance imaging (MRI), psychometric testing, i.e., for perceived mindfulness, stress and emotional eating, food cravings and dietary restraint, and the assessment of body weight prior to and after completing the intervention. Participants were additionally required to report their susceptibility to engage in stress-related overeating behavior. All measures were acquired after a subjectively stressful work or school day and subjects were instructed to abstain from eating for five hours prior to their scheduled measure. After September 2020, participants were required to present a negative SARS-CoV-2 PCR test result obtained on the day of their measure in order to participate in the study. The training programs for both conditions were accessible via an online platform and consisted of 31 sessions delivered in daily portions of 10 to 15 minutes. To promote training adherence, daily reminders were sent to participants by email.

The MMT was developed in close cooperation with Dr. Britta Hölzel who is a mindfulness expert and certified MBSR instructor. In the MMT, participants were provided with a detailed introduction on the theoretical framework of mindfulness while additionally guiding participants through the daily meditation exercises via video or audio- clips. These exercises emphasized the relationship between mindfulness meditation and eating behavior through written instructions encouraging participants to observe their eating behavior and to engage more mindfully with food. The HT condition, on the other hand, was designed to imitate the format of the MMT and provided participants with informative, health-related, video and audio clip excerpts from popular science broadcasting networks in Germany. It is important to note that topics in the HT did not include any information pertaining to mindfulness, meditation, eating behavior, or nutrition. For a detailed description of the training content please see table S1 in the supplementary section. Participants were required to complete at least 27 training sessions to be included in the final analysis.

295 participants were assessed for eligibility and 112 participants fulfilled the inclusion criteria. 87 participants completed the first MRI measure, and 74 participants were also available for the second MRI measure. After preprocessing, data from 66 participants (33 female) participants were

included in the final analysis. A data acquisition flowchart is illustrated in Figure 1. The data acquisition process took place between June 2019 and June 2021.

To verify the pseudo-randomization process, final samples were compared for demographic characteristics, measuring intervals, and an average number of sessions completed using *t*-tests for independent samples or chi-square tests, respectively.

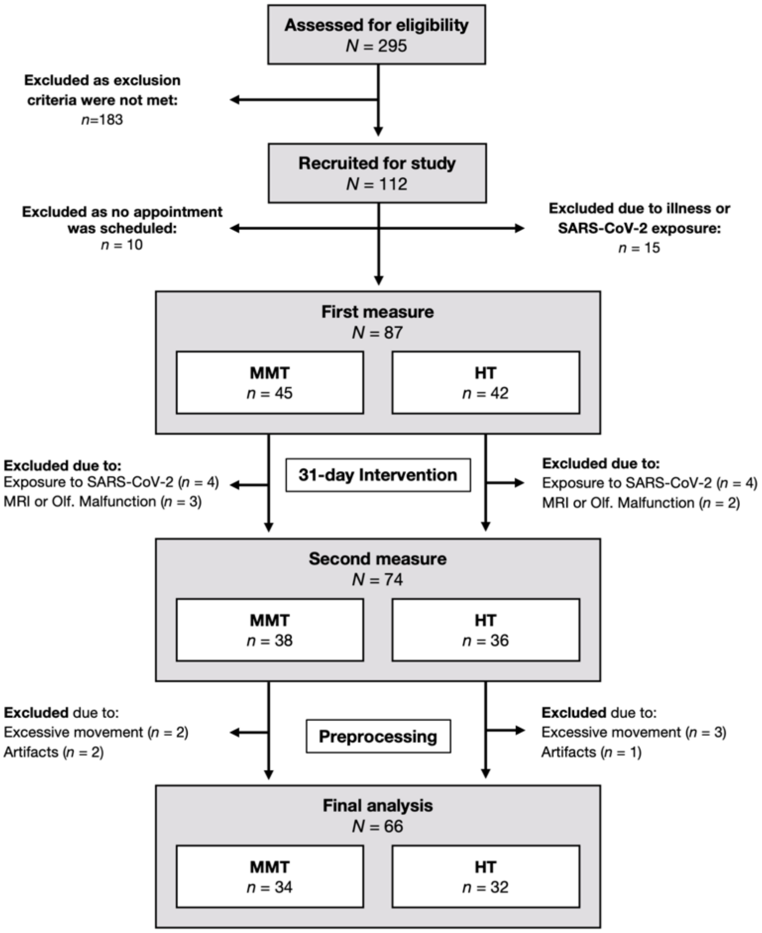

Figure 1: Data acquisition process (June 2019 - June 2021).

Behavioral data

Psychometric testing was conducted using self-report questionnaires which were obtained prior to both MRI measurements. To assess training-related changes in perceived mindfulness, participants completed the German version of the Mindful Attention and Awareness Scale (MAAS) (Brown & Ryan, 2003). The MAAS is a 15-item, self-report scale measuring the intensity of perceived mindfulness in daily life (e.g., *"I find it difficult to stay focused on what is happening in the present"*). The MAAS has been demonstrated to capture training effects in which high scores indicate high levels of perceived mindfulness (Chambers et al., 2008).

An additional variable of interest was the susceptibility to experiencing food cravings as well as the tendency to engage in stress- and emotional-eating. Therefore, German versions of the psychometric assessments of the Food Cravings Questionnaire (FCQ, state and trait), Salzburg Stress Eating Scale (SSES), Salzburg Emotional Eating Scale (SEES), and the Restraint scale were included.

The FCQ is a self-report scale measuring the susceptibility to experiencing food cravings. The FCQ is divided into two subscales; the state scale (FCQ-S), which contains 15 items measuring the current intensity of food cravings (e.g., *"I have an intense desire to eat [one or more specific foods]"*) and the trait scale (FCQ-T), which contains 39 items measuring the general frequency and intensity of food cravings (e.g., "*I feel like I have food on my mind all the time*"). High scores indicate higher susceptibility to food cravings (Cepeda-Benito et al., 2000).

The SSES is a 10-item, self-report, scale measuring the change in eating behavior when under stress (e.g., *"During periods of great stress I eat much more than usual"*). Mean scores above 3 indicate increased food intake when stressed, while scores below 3 indicate decreased food intake when stress (Meule et al., 2018b).

The SEES is a 20-item, self-report scale measuring the change in eating behavior under emotional conditions (e.g., *"When I am anxious, I eat much less than usual"*). Mean scores above

3 indicate an increase in food intake, while scores below 3 indicate a decrease in food intake when emotional (Meule et al., 2018a).

The Restraint Scale is a 10-item, self-report scale measuring weight fluctuation (e.g., *"What is the maximum amount of weight (...) you have ever lost in a month?"*) in addition to the subjective preoccupation with dieting (e.g., *"How often are you dieting?"*). High scores indicate higher levels of dietary restraint which is associated with higher BMI and dysfunctional eating behaviors (Dinkel et al., 2005).

The statistical analyses of behavioral data were performed using SPSS v29.0. The normality of data was assumed as groups were larger than $n = 30$. To assess training effects, psychometric data was entered into a 2 x 2 mixed effects analysis of variance (ANOVA), where group was the between-subject factor and time was the within-subject factor. Results were thresholded at $p < 0.05$.

MRI data acquisition

MRI data were acquired on a 3 T Philips MRI scanner with a 32-channel head coil at Klinikum Rechts der Isar's department of neuroradiology in Munich, Germany.

T2*-weighted resting-state functional images were acquired using echo planar imaging (EPI) with the following scanning parameters: Multiband (MB) factor 2, repetition time (TR) 2.3 s, echo time (TE) 30 ms and flip angle 75°. The field of view (FOV) was set to $(192 \times 192 \times 136)$ mm^3, corresponding to a matrix size of 96×96 with 62 axial slices of $2 \times 2 \times 2$ mm^3 large isotropic voxels. 250 volumes were obtained over the course of approximately 10 minutes. Subjects were instructed to keep eyes closed, to refrain from engaging in any trains of thought as much as possible, and to not fall asleep.

Additional high-resolution T1-weighted anatomical images were acquired using a magnetization-prepared rapid acquisition gradient echo (MPRAGE) sequence with the following scanning parameters: TR 11 ms, TE 5.2 ms and flip angle 8°. 230 axial AC-PC slices encompassing a 384 × 384 matrix of 0.7 × 0.7 × 0.7 mm3 large isotropic voxels were obtained. All anatomical images underwent clinical inspection by a neuroradiological specialist to detect possible structural pathologies.

Preprocessing

Preprocessing was conducted using SPM 12 (The Wellcome Centre for Human Neuroimaging; http://www.fil.ion.ucl.ac.uk/spm). The preprocessing pipeline was created using RestPLUS (Xi-Ze et al., 2019) during which the anatomical image was first coregistered to the mean functional image and segmented into tissue probability maps, which were then used to create a group-specific DARTEL template (Ashburner, 2007). Using these templates, the realigned functional time-series were normalized to MNI space and smoothed using a 4 × 4 × 4 mm^3 full width at half maximum (FWHM) Gaussian Kernel. Additional preprocessing steps were performed using the CONN Toolbox v21.a (Whitfield-Gabrieli & Nieto-Castanon, 2012) and included denoising by regressing out white matter and cerebrospinal fluid using CompCor (Behzadi et al., 2007), filtering time courses with a bandpass filter of 0.01 to 0.1 Hz, as well as de-trending and de-spiking.

Seed-based functional connectivity

Prior evidence demonstrated the differential involvement of hypothalamic and insular subnuclei. Therefore, for each region, four seeds that represented the bihemispheric medial and lateral hypothalamus or the anterior and posterior insula were utilized. Canonical parcellations of the hypothalamus were extracted from the WFU PickAtlas (Maldjian et al., 2003), while parcellations of the insula were extracted from the Hammers Atlas (Hammers et al., 2003). Atlas selection was determined by both the availability and anatomic quality of seeds corresponding to our nuclei of interest. It is important to note that since no single atlas provided seed masks for all regions of interest (ROI), seeds from different atlas sources were selected according to their level of establishment and anatomic correspondence.

The seed-based FC analysis was conducted using the CONN Toolbox. To create first-level connectivity maps, Pearson correlation coefficients between the average time course of voxels within each ROI and every voxel (whole brain) were computed and transformed to z-scores. For the second-level analysis, the resulting maps were entered into a 2 × 2 mixed ANOVA, where training group was the between-subject factor and time was the within-subject factor. Results were simultaneously contrasted at MMT > HT and Post > Pre and thresholded at $p < 0.05$, FDR-corrected for multiple comparisons. To evaluate the directionality of the results, both positive and negative contrasts were applied.

Finally, correlations between changes in FC and behavioral measures for both MMT and HT groups were assessed. For every subject and time point, a mean signal from each significant cluster was extracted from the first-level maps using DPABI V6.0 (Yan et al., 2016). The cluster-specific mean signal from the first time point was subtracted from the mean signal of the second time point, resulting in one value per subject which represented the change in cluster-specific FC after the intervention. Changes in behavioral measures were computed by calculating the difference scores (post-pre-intervention). Both values were then entered into a linear regression in SPSS and thresholded at $p < (0.05 / 2) = 0.025$, Bonferroni corrected for multiple comparisons with two different anatomical ROIs.

Results

Sample characteristics

Groups did not significantly differ in age, gender, years of education (i.e., total number of years spent in school, higher education, or professional training), or BMI. Participants received their second MRI scan no later than 5 days upon completing the training condition.

	Total ($N = 66$)	**MMT** ($n = 34$)	**HT** ($n = 32$)	p value
Age, M ± SD	28.0 ± 5.1	27.4 ± 4.9	28.7 ± 5.3	0.30
Female, n (%)	33 (50)	17 (50)	16 (50)	1.00
Years of education, M ± SD	18.3 ± 3.0	18.2 ± 3.1	18.4 ± 3.0	0.80
BMI, [kg/m^2], M ± SD	24.1 ± 4.1	23.4 ± 4.3	25.0 ± 3.9	0.12

Table 1: Participant demographics.

Behavioral data

Upon completing the training conditions, both groups displayed a slight decline in body weight. This change, however, was not statistically significant for either group.

In line with our hypotheses, the MMT was found to effectively increase levels of perceived mindfulness demonstrated via an increase in MAAS scores upon completing the intervention ($M_{Pre} = 53.9$, $SD = 10.6$; $M_{Post} = 57.9$, $SD = 8.7$). No increase in perceived mindfulness was observed in participants of the HT ($M_{Pre} = 55.5$, $SD = 12.6$; $M_{Post} = 54.9$, $SD = 11.6$). An ANOVA was conducted and determined a significant group-by-time interaction ($F\ (1,64) = 7.74$, $p = 0.007$, partial $\eta^2 = 0.108$).

Following the MMT, participants also reported lower FCQ-T scores indicating an overall reduction of food cravings ($M_{Pre} = 84.0$, $SD = 30.3$; $M_{Post} = 55.6$, $SD = 27.9$). In the HT condition, FCQ-T scores demonstrated no significant difference upon completing the training ($M_{Pre} = 79.4$, $SD = 34.6$; $M_{Post} = 78.0$, $SD = 36.0$). An ANOVA was conducted and resulted in a significant group by time interaction ($F\ (1,64) = 20.60$, $p < 0.001$, partial $\eta^2 = 0.243$).

Furthermore, the MMT resulted in a significant reduction of stress- and emotional- eating as assessed by the SSES ($M_{Pre} = 33.7$, $SD = 8.1$; $M_{Post} = 31.8$, $SD = 6.7$) and SEES ($M_{Pre} = 64.3$, $SD = 7.1$; $M_{Post} = 58.4$, $SD = 9.2$). Participants of the HT, however, did not demonstrate any significant changes in stress-eating ($M_{Pre} = 32.4$, $SD = 9.9$; $M_{Post} = 31.8$, $SD = 10.5$) or emotional-eating behavior ($M_{Pre} = 61.8$, $SD = 10.0$; $M_{Post} = 60.2$, $SD = 10.7$). Again, an ANOVA was conducted and determined a significant group-by-time interaction for both the SSES (F $(1,64) = 4.06$, $p = 0.048$, partial $\eta^2 = 0.06$) and SEES (F $(1,64) = 4.94$, $p = 0.030$, partial $\eta^2 = 0.072$) questionnaires. It is important to note that a Levene's test revealed that the homogeneity of error variances was not given for data pertaining to $\text{SSES}_{\text{Post}}$ and SEES_{Pre}. While it has been argued that the results deriving from data of failed homogeneity of error variance still allows for sufficient inferencing (Hsu, 1996), we repeated the analysis by comparing individual difference scores with t-tests for independent samples between groups. Results for the SSES (t $(64) = 2.02$, two-sided $p = 0.048$) and the SEES (t $(64) = 2.22$, two-sided $p = 0.030$) remained consistent, thereby confirming the results of the prior analysis.

No significant group effects of the MMT on dietary restraint as measured by the Restraint scale were observed (F $(1,64) = 3.174$, $p = 0.080$, partial $\eta^2 = 0.047$).

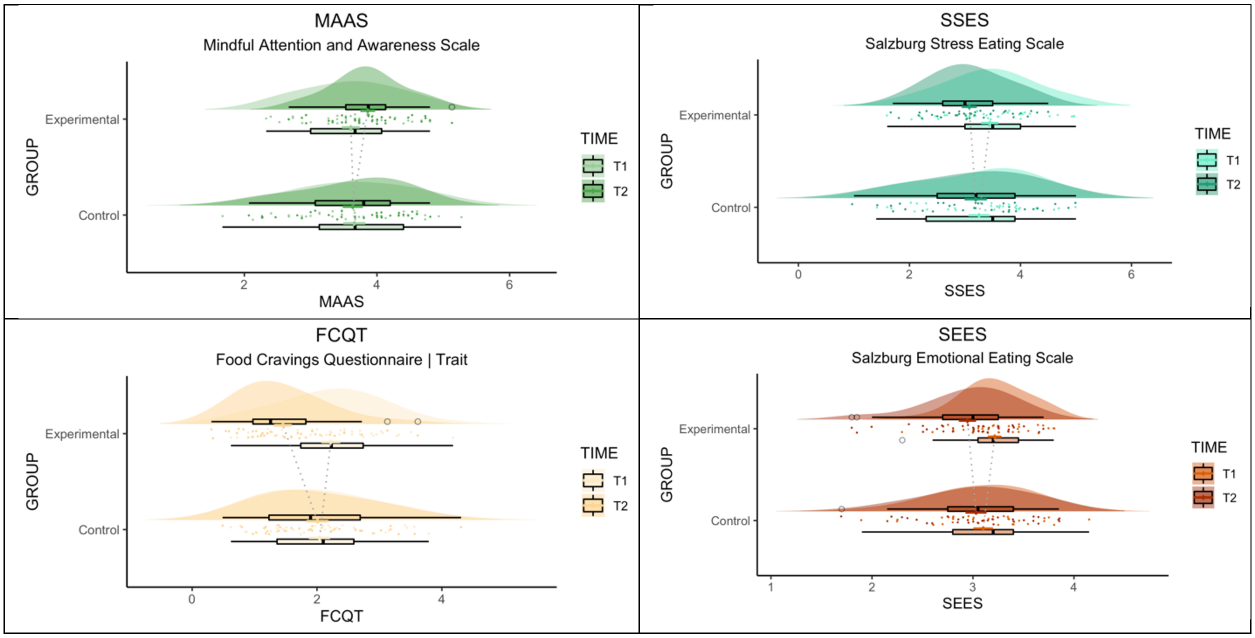

Figure 2: visualizes the change in various self-report measures between T1 (pre-intervention) and T2 (post-intervention). *Experimental group* = MMT; *Control group* = HT

			Peak MNI coordinates					
ROI		**Cluster region**	***x***	***y***	***z***	***k***	p_{FWE}	p_{FDR}
Hypothalamus	L. Lateral	L. PreSMA	-18	10	60	49	0.047	0.042
	R. Lateral	R. Ventral PCC	-14	-58	10	131	0.081	0.027
	L. Medial	L. Striatum/Thalamus	-16	-16	-4	137	0.03	0.033
	L. Medial	L. Precuneus	4	-82	34	297	0.00025	0.00023
	L. Medial	L. Caudal Precuneus	8	-52	64	119	0.15	0.033
	L. Medial	L. Angular Gyrus	46	-46	16	128	0.10	0.037
Insula	L. Anterior	L. Postcentral Gyrus	-52	-20	46	329	0.00002	0.000001
	L. Anterior	R. Postcentral gyrus	48	-74	-6	150	0.07	0.03
	L. Anterior	Temporal Lobe / Occipital Cortex	44	-26	-52	143	0.10	0.02
	L. Posterior	L. Postcentral Gyrus	-46	-30	48	167	0.046	0.034
	R. Posterior	L. Inferior Parietal Lobe	48	-32	32	337	0.003	0.002

Table 2: ANOVA results with associated anatomic regions. *(k = Number of voxels in cluster; R = Right hemispheric; L = Left hemispheric, PreSMA = Pre-supplementary motor area, PCC = Posterior cingulate cortex)*

The interaction results of the 2 x 2 ANOVA from the whole brain, FDR-corrected analyses revealed significant changes in hypothalamic and insular FC in participants of the MMT group whereas no changes in FC were observed in the HT group.

The analyses using the left medial hypothalamus as a seed region demonstrated FC increases with two clusters within the right precuneus and an additional cluster within the right angular gyrus. FC analyses using the left medial hypothalamus demonstrated decreases in FC with a cluster extending across the left dorsal striatum and thalamus. The analyses conducted with the right lateral hypothalamus exhibited increased FC with a cluster within the vPCC, whereas the analyses conducted with the left lateral hypothalamus yielded decreased FC with the left pre-supplementary motor area.

Additional FC increases were observed between the left anterior insula and bilateral clusters within the postcentral gyrus as well as a cluster within the right occipital gyrus. Increased FC was also observed between the left posterior insula and the left postcentral gyrus in addition to observing increases in FC between the right posterior insula and the right inferior parietal lobule. An overview of the FC results can be seen in Figure 3.

Interestingly, changes in hypothalamic connectivity patterns in the MMT group (but not the HT group) were accompanied by a multitude of changes on the behavioral level (Table 3). For example, greater decoupling of FC between the left medial hypothalamus and the left dorsal striatum and thalamus significantly correlated with a greater reduction of FCQ-T scores. Additionally, SSES scores were inversely correlated with an increase FC between the right lateral hypothalamus and the vPCC. These results indicate that the greater the decline in stress eating behavior, the greater the increase in FC between the lateral hypothalamus and the vPCC was observed. Furthermore, our results demonstrated that an in increased MAAS scores correlated significantly with increased FC between the left medial hypothalamus and the right caudal precuneus, whereas a negative correlation between MAAS score and an increase in FC between the left medial hypothalamus and the right angular gyrus was observed.

It is important to note that FC changes of the insula did not correlate with any of the changes of behavioral measures, nor were any significant correlations observed between FC changes and behavioral measures of the HT group.

Hypothalamus	Cluster region	MAAS		FCQT		SEES		SSES	
L. Lateral	L. PreSMA	r^2	-0.06	r^2	0.01	r^2	-0.01	r^2	0.01
		p	<0.23	p	<0.88	p	<0.86	p	<0.94
R. Lateral	R. Ventral PCC	r^2	0.15	r^2	0.10	r^2	-0.27	**r^2**	**-0.47**
		p	<0.74	p	<0.66	p	<0.32	**p**	**<0.03***
L. Medial	L. Striatum/Thalamus	r^2	-0.04	**r^2**	**0.37**	r^2	-0.09	r^2	0.27
		p	<0.94	**p**	**<0.01****	p	<0.27	p	< 0.69
L. Medial	L. Precuneus	r^2	0.04	r^2	-0.02	r^2	0.04	r^2	0.01
		p	<0.05	p	<0.21	p	<0.24	p	<0.81
L. Medial	L. Caudal Precuneus	**r^2**	**0.34**	r^2	-0.19	r^2	0.05	r^2	0.05
		p	**<0.05***	p	<0.22	p	<0.24	p	< 0.82
L. Medial	L. Angular Gyrus	**r^2**	**-0.34**	**r^2**	**-0.30**	r^2	-0.12	r^2	0.01
		p	**<0.03***	**p**	**<0.05***	p	<0.61	p	< 0.87

Table 3: Results of linear regression between the change in functional connectivity and the change in behavioral measures. *(MAAS = Mindful Attention and Awareness Scale, FCQT = Food Cravings Questionnaire – Trait, SEES = Salzburg Emotional Eating Scale, SSES = Salzburg Stress Eating Scale, R = Right hemispheric; L = Left hemispheric, PreSMA = Pre-supplementary motor area, PCC = Posterior cingulate cortex)*

Discussion

This study investigated the effects of a food-related mindfulness training on eating behavior. Our results successfully demonstrate that MMT can reduce stress-eating tendencies while also increasing perceived mindfulness. In fact, the observed behavioral changes pertaining to both mindfulness and eating behavior significantly correlated with FC alterations demonstrating increased and decreased coupling of brain areas relevant to eating behavior, self-referential thinking and mind-wandering, reward perception, and the processing of sensory stimuli in the environment. Our results thereby provide insight into the behavioral and neuronal mechanisms underlying the positive impact mindfulness meditation has on stress-eating.

Self-Report Measures:

Through the administration of self-report measures, this study was able to determine the effects of a food-related MMT on perceived eating behavior and mindfulness. Not only were we able to demonstrate a significant reduction in perceived stress-eating, emotional eating, and food cravings, but we were also able to observe an increase in perceived mindfulness in daily life. Our findings are, therefore, in line with prior observations supporting the positive effects MMT has on stress, emotion regulation, interoceptive awareness, and perceived mindfulness (Chiesa & Serretti, 2009; Fissler et al., 2016; Kabat-Zinn, 2003b; Khoury et al., 2015; Roemer et al., 2015; Teper et al., 2013). Given that the MMT was conducted entirely online, our results contribute to the literature on the effectiveness of web-based MMT, while also providing specific evidence on its ability to reduce stress-eating behavior without any in-person components. Further research is, however, required to determine whether the effectiveness of web-based MMTs differ from interventions with in-person training, as well as whether web-based MMTs can be utilized as a therapeutic mechanism for individuals with obesity or for those suffering from metabolic or cardiovascular disease.

To this end, not only was the present study able to demonstrate MMT-elicited changes in self-reported, behavioral, measures, but we were also able to demonstrate changes on the neuronal level exhibited by resting-state FC changes in brain areas essential in regulating hunger and satiety cues, namely the hypothalamus and the insula.

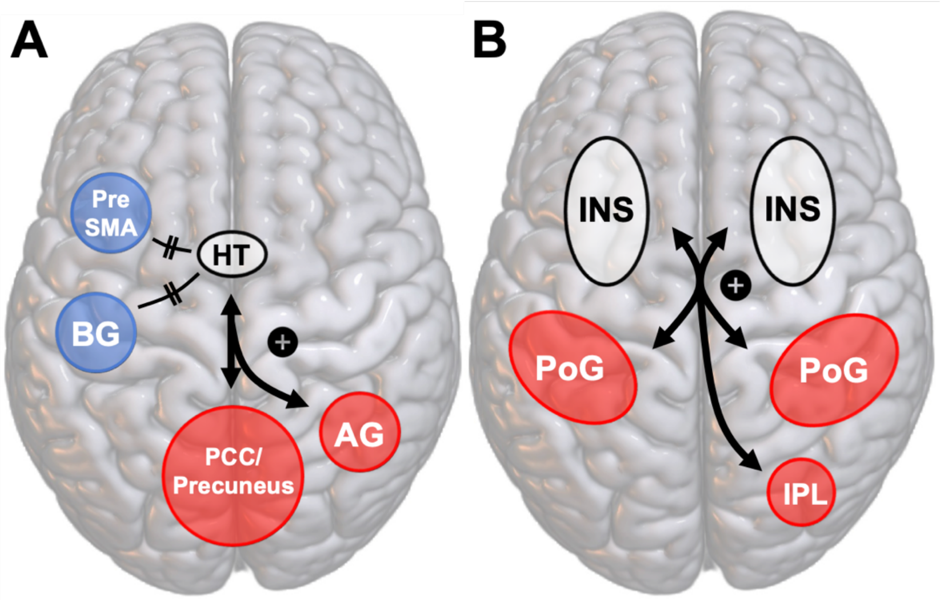

Figure 3: depicts and overview of the FC changes observed between the hypothalamus (A), the insula (B), and the whole brain. HT = hypothalamus; BG = basal ganglia; PreSMA = Pre supplementary motor area; PCC = precuneus; AG = angular gyrus; INS = insula; PoG = Postcentral gyrus; IPL = inferior parietal lobe.

Hypothalamus:

The hypothalamus plays a critical role in regulating the body's stress response in addition to eating behavior (Bose et al., 2009; Holmes et al., 2010; Kuo et al., 2007; McEwen, 2007; McEwen & Stellar, 1993; Sojcher et al., 2012). To observe the processes underlying perceived hunger and satiety, the hypothalamus can be parcellated into the lateral and medial hypothalamus. These nuclei have been attributed to the processing of perceived hunger and satiety levels, respectively (Aston-Jones et al., 2009; Bernardis & Bellinger, 1996; Saper et al., 2002; Syan et al., 2021). In participants of the MMT group, the FC of the hypothalamus was subject to an array of changes following MMT.

Mindfulness Meditation & the DMN

The results of this study were able to demonstrate an increase in FC between subregions of the hypothalamus and multiple clusters within the precuneus, vPCC, and angular gyrus in the MMT group. Interestingly, these clusters all pertain to hub regions of the DMN, which is one of the most extensively studied large-scale brain networks. The DMN is frequently associated with the mental processes of self-referential thinking and mind-wandering (Menon, 2011). Prior research was able to demonstrate that mindfulness and similar meditation practices have a wide-ranging impact on the DMN. For example, in comparison to meditation-naïve individuals, studies were able to determine that experienced meditators yielded less connectivity between core hubs of the DMN, which formally indicates an overall reduction of network activation (Brewer et al., 2011). In addition, a growing body of evidence suggests that mindfulness meditation increases connectivity between the DMN and other networks, especially the salience network (SN) (Bremer et al., 2022; Rahrig et al., 2022), which encompasses hub regions responsible for detecting emotional and sensory information (Menon, 2011). Notably, a recent, extensive systematic review observing the resting-state FC changes as an outcome of MMT published by Rahrig et al. (2022)

found increased network connectivity in the DMN as well as the SN. Connectivity increases between brain networks such as the DMN and SN can, therefore, be interpreted as an increase in awareness as a result of regular mindfulness meditation practice (Bremer et al., 2022). Similarly, increased connectivity between hub regions of the DMN and the hypothalamus could indicate that a food-related MMT facilitates the more conscious perception of hunger and satiety. This could ultimately reflect increased interoceptive awareness, a cognitive process fundamental in the regulation of eating behavior.

Remarkably, our findings were corroborated by correlations observed between alterations in FC and behavioral changes. To this end, increased FC between the medial hypothalamus and the caudal precuneus positively correlated with an increase in MAAS scores. An increase in self-reported mindfulness is, therefore, associated with stronger coupling between the medial hypothalamus (relevant for the processing of satiety along with other homeostatic processes), and the caudal precuneus (relevant for self-reflection). Therefore, when individuals perceive themselves to be more mindful, the processing of satiety cues may be more strongly linked with self-referential processing.

An additional negative correlation between an increase in FC between the lateral hypothalamus and the vPCC with the reduction in SSES was observed. This suggests that the greater increase in FC between these brain areas, the less participants were inclined to succumb to stress-eating. Taken together, our findings indicate that MMT strengthens the interaction between hub regions of the DMN and the hypothalamus which goes along with increased levels of perceived mindfulness and a reduction in stress-eating behavior.

Mindfulness Meditation & the Reward System

Not only does our web-based, food-related, MMT implicate areas of the DMN, but we were also able to observe MMT's influence on areas of the reward system. To this end, an additional FC alteration was observed between the left medial hypothalamus and the left dorsal striatum. The dorsal striatum has been demonstrated to elicit cravings and reward-seeking behaviors (Grall-Bronnec & Sauvaget, 2014). Interestingly, the dorsal striatum is also said to be responsible for triggering relapse during abstinence in addiction (Grall-Bronnec & Sauvaget, 2014). Therefore, a reduction in FC between the medial hypothalamus and the dorsal striatum could indicate a decoupling of brain areas responsible for processing feelings of satiety and reward. Notably, a significant, positive, correlation between the observed reduction in FC between these two brain areas and the FCQ-T was observed. This association indicates that greater reduction in FC between the lateral hypothalamus and the dorsal striatum was associated with a greater reduction in food cravings in participants of the MMT group. These results could imply that feelings of satiety may be perceived as less rewarding, which could consequently reduce the tendency to develop food cravings.

Overall, the findings pertaining to the hypothalamus and areas of the DMN support MMT's role in cultivating a more mindful relationship with food. Interestingly, our results go in line with another recent systematic review conducted by Syan et al. (2021). The main aim of this review was to define the differences in FC patterns in individuals with obesity in comparison to controls. Syan et al. (2021) determined that the existing literature supports differences in resting-state FC in individuals with obesity. For example, aberrant DMN connectivity (i.e., hypoconnectivity), as well as increases in FC between the hypothalamus and regions attributed with reward, limbic, and salience networks were observed, while also demonstrating a decrease in FC between the hypothalamus and cognitive regions. Although the individuals recruited for the present study had a BMI within, what is considered to be, a healthy range, our results were also able to indicate MMT elicited FC changes in stress eaters.

Not only did our results demonstrate FC changes between subregions of the hypothalamus and hub regions of the DMN and reward areas, but we were also able to observe FC changes between the medial hypothalamus and the angular gyrus (AG). The AG is said to play a role in the integration of sensory information, specifically the perception of smell and taste as it receives input from both the olfactory and gustatory cortices, which are essential in processing the smell and taste of food (Contreras-Rodriguez et al., 2020). These results indicate an increased coupling between brain areas demonstrated to be involved in the processing of perceived satiety and integrating perceptual information, respectively. Interestingly, the correlation analysis conducted between FC and behavioral measures demonstrated a significant negative correlation indicating that a greater increase in FC between the medial hypothalamus and the AG is associated with a greater reduction in food cravings (via the FCQ-T). These results indicate that the greater the coupling between the medial hypothalamus and the AG, the greater the reduction of stress-eating behaviors in mindfulness practitioners.

Mindfulness Meditation & Reducing Automatic Eating Behavior

In addition to the observed changes between the hypothalamus and hub regions of the DMN, reward areas, as well as areas involving sensory integration, our results could demonstrate alterations in FC between the hypothalamus and areas pertaining to automatic eating behaviors. For example, we observed a reduction in FC between the left lateral hypothalamus and the left pre-supplementary motor area (PreSMA). The PreSMA is a brain region demonstrated to play a key role in regulating movement, motor planning, and reward behavior (Nachev et al., 2007; Tabu et al., 2011). Given the observed reduction in FC between these brain areas, our results indicate that MMT may reduce the automatic, action-oriented, behaviors when hunger is perceived. This could be attributed to more reflective decision-making about perceived hunger elicited via MMT prior to engaging in goal-directed behavior to find or eat food.

Overall, our results pertaining to the hypothalamus demonstrate MMT elicited resting-state FC changes between the subregions of the hypothalamus, key nodes of the DMN, in addition to areas processing reward, sensory integration, and action-oriented behaviors. These results emphasize MMT-elicited network changes in structures known to be involved in food cravings and eating behavior.

Insula:

Not only were we able to observe differences in FC using the hypothalamus as a region of interest, but we were additionally able to show MMT-associated FC changes with the insula. The insula has been demonstrated to be involved in interoception, or the perception of bodily sensations, in addition to attentional control which both play an essential role in mindfulness meditation and eating behavior, specifically in the subjective experience of flavor, texture, and smell (Craig, 2009; Critchley et al., 2004; Frank et al., 2013; Nelson et al., 2010; Roy-Côté et al., 2021; Terasawa et al., 2011; Torske et al., 2022).

Similar to the hypothalamus, the insula can be parcellated into individual nuclei allowing for the inspection of its distinct roles in the processing mindfulness and stress-related eating behavior. While the anterior insula has been demonstrated to be involved in mindfulness through its integration of interoceptive awareness and emotion regulation (Craig, 2009; Critchley et al., 2004), the posterior insula has been linked to the processing of somatosensory information, particularly the awareness of bodily sensations (Rolls, 2006). The anterior and posterior insula were, therefore, selected as seed regions of interest with the aim of investigating potential FC changes, to ultimately gain insight into the neural impact of a food-related MMT.

Mindfulness Meditation & Sensory Awareness:

The results of this analysis demonstrated an MMT-associated increase in FC between both the anterior and the posterior division of the insula and nearly symmetrical, bilateral, clusters within the postcentral gyrus. The postcentral gyrus, or primary somatosensory cortex, receives sensory information via thalamocortical pathways; sensory input is organized topographically with tactile information originating from facial and oral sensations processed in the lateral postcentral gyrus which is where the clusters were observed (Grabenhorst & Rolls, 2014).

Given the emphasis MMT puts on the conscious perception of bodily sensations, it seems only plausible that areas responsible for perceiving somatosensory sensations in addition to areas that integrate the sensations into awareness are simultaneously activated. This interpretation would thereby support the observed increase in FC in participants that completed the MMT. The localization of the clusters within regions responsible for facial and oral sensations could be explained by the emphasis our food-specific MMT puts on increasing the awareness of food and its accompanying sensations while it is being consumed. As it is known that regions and networks involved in sensory processing are stably active (also during rest), participants in the 31-day food-related MMT could demonstrate an increase in activation and connectivity within and between sensory areas pertaining to eating behavior at rest. In addition, the insula has been identified as part of the primary gustatory cortex, thus being responsible for the perception of taste (Iannilli et al., 2014). An increase in the interaction between areas of the primary gustatory cortex and areas of the postcentral gyrus suggests an increase in the integration of the sensory components, i.e., texture and taste, involved in the sensation of eating. Additional connectivity increases between the posterior insula and the supramarginal gyrus, an area associated with the somatosensory cortex, provides further evidence for the MMT-elicited integration of components involved in the processing of sensations. These results indicate that a food related MMT can increase the efficiency of sensory integration and its corresponding networks all while facilitating increased awareness during eating.

While the anterior and posterior regions of the insula were found to display increased FC with the postcentral gyrus, additional connectivity increases, specific to its subdivisions, were observed. For instance, an increase in FC was observed between the anterior insula and the medial temporal lobe (MTL). While previous research has demonstrated the MTL to play an essential role in the memory formation and retrieval (Henson, 2005), a transcranial magnetic stimulation (TMS) study published in 2015 (Gonzalez-Franco, 2015) demonstrated that the temporary disruption of the MTL led to increased consumption of high-calorie foods. Therefore, our observed increase in FC (as opposed to a disruption in the MTL via TMS) could corroborate these findings through our observed reduction in stress-eating tendencies. Furthermore, we were able to observe an increase in FC between the anterior insula and the occipital lobe, or visual cortex. The human sense of sight additionally provides valuable information about food cues in the environment thereby influencing food selection and eating behavior. The observed increase in FC between the anterior insula, which integrates sensory information into a representation of interoceptive awareness, and the visual cortex, may therefore indicate increased awareness of visual food cues in the environment. Given that the FC observed together with the insula involved brain regions essential in sensory processing and sensory integration, a plausible explanation as to why no significant correlations between FC and self-report measures were observed (as was observed between the hypothalamus and self-report measures) may be due to the fact that our self-report measures did not specifically observe behavioral changes in sensory perception, specifically to the sensory perception of food. In future studies, it would be interesting to observe where MMT elicits changes in sensory persecution (i.e., olfaction and gustation). Nevertheless, the insula, and its ROI subdivisions, provide insight into MMT's ability to alter FC pertaining specifically to the processing of sensory stimuli, which can consequently alter eating behavior.

Overall, the observed MMT- associated FC changes utilizing both the hypothalamus and the insula and their individual nuclei, provides evidence pertaining to MMT's ability to alter resting-state FC pertaining to the DMN (i.e., self-referential thinking and mind-wandering), reward perception, and the processing of sensory stimuli in the environment, in addition to providing evidence on MMT's ability to reduce stress- and emotional-eating tendencies.

Limitations:

The results of this study must be interpreted under the consideration of methodological limitations. First, given our hypothesis-driven approach and the a-priori selection of seed regions, inevitably entails the risk of overlooking other, potentially relevant, interactions. Nevertheless, the existing literature suggests that the hypothalamus and insula effectively provide a relevant perspective on both mindfulness and eating behavior. Therefore, we believe that the results generated from the present study allow for a better understanding of the mechanisms underlying the intersection of mindfulness and eating behavior. While we acknowledge the complex nature of both eating behavior and mindfulness meditation, and therefore would not rule out the possibility of further relevant influences, a possible strategy to investigate this subject matter further would be to utilize data-driven methods, e.g., independent component analyses. However, these analyses typically involve strict statistical thresholding and, therefore, may not capture subtle effects.

Moreover, it is important to note that not all the results withstood multiple comparison correction. While it would be a considerable alternative to liberalize thresholding, we believe that the recurrent patterns across ROIs, along with the statistical interdependence with behavioral measures, gives sufficient grounds to assume plausibility of these results.

Finally, we would like to point out that the instructions given to participants during the imaging procedure, i.e., to keep their eyes closed and not engage in a specific train of thought, does not exclude the possibility of entering a meditative state during the MRI measure. Therefore, despite our instruction, we cannot distinguish whether the observed effects occur at rest or during meditation. Nevertheless, we believe that our results convey valuable information on how MMT influences the functional organization of the brain and, thereby, cultivates a healthier relationship with food.

Conclusions

Stress can elicit a series of psychological and physiological responses that can ultimately lead to stress-related overeating behavior. Frequently engaging in stress-eating tendencies can result in persistent weight gain which can cause metabolic and cardiovascular disease. The aim of this study was, therefore, to investigate whether a food-related mindfulness training can effectively reduce stress-related overeating tendencies. Our results were not only able to demonstrate the successful increase in perceived mindfulness but also to observe the reduction in stress-eating and emotional-eating tendencies, as well as the reduction of food cravings. Our analyses investigating the neural underpinnings of mindfulness training and its influence on stress-eating behavior ultimately demonstrate altered FC patterns within the DMN, reward processing, and sensory processing upon completing a food-related mindfulness training. Additionally, our results provide novel insight into the relationship between stress, stress reduction, and mindfulness training on both the behavioral and neuronal levels. This study, therefore, serves as evidence of the effectiveness of MMT as an intervention strategy for stress-eating behavior and should be considered for therapeutic or preventative treatment programs.

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5.0 General Summary

This dissertation project was successfully able to provide insight into the effects of MMT as an intervention strategy for stress-related overeating behavior through the implementation of two clinical trials. Not only were the results of this dissertation project able to provide evidence on the effectiveness of web-based MMT on the behavioral and neuronal levels through the first clinical trial, but this dissertation project was additionally able to statistically locate the neural processing nodes of the olfactory cortex relevant for the processing of food stimuli. Finally, by conducting a second clinical trial, this dissertation provides insight into the effects of a web-based, food-related, MMT on stress-eating behavior by demonstrating changes observed on both the behavioral and neuronal levels. The results of the projects presented in this dissertation will not only contribute to the literature on stress, stress-eating, as well as MMT, but could also help prevent the consequences resulting from maladaptive overeating behavior. To this end, the relevance of this dissertation project remains high when considering the increasing global prevalence of stress-related overeating and its resulting metabolic and cardiovascular diseases.

In summary, this dissertation provides evidence of the effectiveness of MMT as an intervention strategy for stress and anxiety reduction as well as the reduction of stress-eating behavior and should therefore be considered for therapeutic or preventative treatment programs.

5.1. The Effects of a Web-Based MMT: Project 1

Within the scope of this dissertation, Project 1 aimed to investigate the effects of a 31-day web-based MMT on attention, mental health, as well as brain structure and function. Given that the available research pertaining to the effectiveness of web-based MMT, in addition to research investigating the relationship between MMT, decreased stress and anxiety levels, and improved cognitive function is limited, the results of Project 1 provide valuable information on MMT to the scientific community.

Not only did Project 1 demonstrate that MMT leads to improvements in perceived anxiety levels, perceived stress, attentional performance, and flow experience, but it was also able to demonstrate MMT-induced changes in brain activation, specifically in the left superior frontal gyrus (SFG), posterior cingulate cortex (PCC), and right hippocampus. Interestingly, these changes were accompanied by increased microstructural integrity between the right hippocampus and the superior frontal gyrus. These findings are noteworthy given the initial interest in studying the effects of MMT on attention. For example, the PCC has not only been previously associated with cognitive and executive functioning but it has also been associated with the frontoparietal control network as well as the dorsal attention network, which are both fundamental in the processing of visuospatial attention (Leech & Sharp, 2014; Leech & Smallwood, 2019; Somers & Sheremata, 2013). These results are particularly important within the scope of this dissertation project given that attention is a cognitive process that has been demonstrated to be severely impacted by stress and anxiety (Liu et al., 2020; Robinson et al., 2013).

Interestingly, not only did our results capture improvements in attentional processing, but we were also able to observe a significant, MMT-induced increase in flow experience. These findings imply that MMT can have an effect on both attentional mechanisms as well as on the psychological flow state. In fact, our results reflect a recent publication from Xie (2022) in which increased flow experience, teamwork abilities, and productivity were associated with MMT. Similarly, our results highlight the potential of a web-based MMT to elicit positive changes in perceived stress, flow experience, and attention, all while demonstrating its impact on the neuronal level.

It is, however, important to note that Project 1 was not able to demonstrate a significant reduction in self-reported stress levels in the MMT group. However, our results could demonstrate a negative correlation between hippocampal activation and the PSS score upon completing the MMT. This finding indicates that greater stress reduction was associated with greater hippocampal activity, thereby implicating the hippocampus in modulating the behavioral adaptation to stress. This interpretation of the results would reflect the findings observed by Fanselow and Dong (2010).

Not only do the results of Project 1 demonstrate an associated between stress and hippocampal activity during an attention task but increases in white matter microstructural integrity were also observed in the right uncinate fasciculus (rUNC). These results indicate that MMT strengthened the connection between the hippocampus and areas of the frontal lobe, thereby further emphasizing MMT's role in emotion regulation and reducing perceived stress levels. In addition, given that changes were observed both in hippocampal structure and function while also observing correlations with self-report measures, these results could indicate that the hippocampus may mediate the relationship between MMT and stress reduction.

Project 1 was ultimately able to contribute to the understanding of the neural mechanisms of MMT on attention, in addition to its impact on flow, stress, and other psychological outcomes. Based upon these findings, a similar web-based MMT was utilized in dissertation Project 3 to continue to investigate the effectiveness of web-based MMT on a specific subset of the population, namely on individuals who engage in stress-related overeating behaviors.

5.2 Localizing the Olfactory Cortex: Project 2

The olfactory cortex and the ability to smell are considered to be one of the oldest, evolutionary, sensory systems that enable organisms to find food, mates, and avoid predators (Hoover, 2010). Given our interest in investigating the effects of web-based MMT on eating behavior, the aim of Project 2 was to identify the functional neural anatomy of food odor processing. To achieve this aim, all available and relevant literature pertaining to the investigation of the olfactory cortex via fMRI was utilized to quantify inter-study concordance to generate activation probability maps as well as identify the individual processing nodes for different odor categories (i.e., pleasant, aversive, food, and all odors).

Interestingly, one of the more prominent findings pertaining to the food odor ALE was the observed activation in the insula. This finding can be explained given the multisensory nature of food stimuli and the insula's role in integrating multisensory stimulation (Lundström et al., 2011). When engaging with a food stimulus in the environment, not only is the sense of smell utilized to assess the edibility of the food, but the brain is simultaneously processing visual inputs as well as gustatory and somatosensory stimulation during the consumption and evaluation of food. Therefore, the insula, known for its role in integrating multisensory stimuli, regulating energy balance, appetite (Frank et al., 2013), and processing sensory stimuli (Berthoud & Münzberg, 2011), serves as an excellent candidate for the observation of MMTs effects on stress-eating behavior.

The results of Project 2 not only provide activation probability maps for all odors, aversive odors, and pleasant odors, but the results of the food odor ALE provided specific information on the functional neural cortex of food stimulus processing and was therefore utilized in the subsequent analyses of this dissertation project.

5.3 Mindfulness Reduces Mindless Eating: Project 3

Within the scope of this dissertation, Project 3 aimed to examine the effects of a food-related MMT on eating behavior and its underlying neural mechanisms. The results demonstrate that a food-specific MMT was successfully able to reduce stress-eating tendencies in addition to increasing perceived mindfulness. Our findings are in line with prior observations supporting the positive effects MMT has on stress, emotion regulation, interoceptive awareness, and perceived mindfulness (Chiesa & Serretti, 2009; Fissler et al., 2016; Kabat-Zinn, 2003b; Khoury et al., 2015; Roemer et al., 2015; Teper et al., 2013). Further strengthening the results we observed on the behavioral level, the neuroimaging analyses, which focused on seed regions fundamental in the processing of perceived hunger, stress, and emotion regulation, revealed noteworthy FC changes. For example, increased FC between the hypothalamus and hub regions of the DMN were observed. While the hypothalamus plays a critical role in regulating the body's stress response in addition to eating behavior (Bose et al., 2009; Holmes et al., 2010; Kuo et al., 2007; McEwen, 2007; McEwen & Stellar, 1993; Sojcher et al., 2012), the DMN is frequently associated with the mental processes of self-referential thinking and mind-wandering wandering (Menon, 2011). In fact, a growing body of evidence suggests that MMT increases FC between the DMN and other networks, such as the salience network (SN) (Bremer et al., 2022; Rahrig et al., 2022). Our results, therefore, indicate an increase in coupling between brain areas responsible for the processing of stress, perceived satiety, and self-referential processing, which could indicate that a food-related MMT facilitates the more conscious perception of hunger and satiety.

The changes observed on the neuronal level were remarkably correlated with MMT-induced behavioral changes. For example, an increase in MAAS score was positively correlated with an increase in FC between the medial hypothalamus and the caudal precuneus, whereas a negative correlation was observed between the lateral hypothalamus and vPCC and a reduction in SEES score. Taken together, these observations suggest that the MMT increases the connectivity between hub regions of the DMN and the hypothalamus which goes along with increased levels of perceived mindfulness and a reduction in stress-eating behavior.

Additionally, changes between the hypothalamus and brain areas relating to reward regions were also observed thereby suggesting a decoupling of the processing of perceived satiety and reward-seeking behaviors, specifically between the left medial hypothalamus and the left dorsal striatum, which could indicate a decoupling of brain areas responsible for processing feelings of satiety and reward (Grall-Bronnec & Sauvaget, 2014).

Furthermore, MMT was associated with increased FC between the insula and regions involved in sensory processing. This suggests that MMT enhances sensory awareness through the integration of tactile, gustatory, and visual information. This finding is significant given that, the insula has been identified to be part of the primary gustatory cortex, thus being responsible for the perception of taste (Iannilli et al., 2014). An increase in the interaction between areas of the primary gustatory cortex and areas relevant for sensory processing suggests an increase in the integration of the sensory components, i.e., texture and taste, upon completing MMT.

Lastly, FC changes between the insula and brain regions involved in memory formation and retrieval, as well as visual processing were observed. As the human sense of sight can provide information pertaining to food cues in the environment, MMT's ability to influence sensory perception, in addition to increasing the awareness of food cues in the environment, continues to support MMT’s influence on eating behavior.

Dissertation Project 3 could provide insight into MMT's ability to increase perceived mindfulness while reducing food cravings and stress- and emotional-eating tendencies. It could also provide insight into the neural underpinnings underlying MMT and its influence on stress and eating behavior.

Given that the MMT was conducted entirely online, our results additionally contribute to the literature on the effectiveness of web-based MMT and, therefore, also support the utilization of web-based MMT as an intervention strategy for stress reduction that can influence eating behavior. Web-based MMT should, therefore, be considered for therapeutic or preventative treatment programs.

6.0 Limitations and Methodological Considerations

6.1 Participant Recruitment | Baseline Scores

Interestingly, despite the similarities in web-based MMT interventions utilized in Projects 1 and 3, one of the most striking differences in the results was observed in the MAAS self-report measure. The MAAS questionnaire evaluates perceived mindfulness in daily life, and while in Project 3, a significant increase in perceived mindfulness was observed upon completing the food-related MMT, this was not the case upon completing the MMT in Project 1. One methodological factor that may explain these observed differences in the MAAS self-report measure is participant recruitment. While participants with a high perceived stress score were recruited to participate in Project 3, stress scores were not evaluated as a part of the inclusion criteria for the recruitment process in Project 1. Therefore, the baseline stress score may have had an influence on the overall effect of perceived mindfulness. In fact, a recent study conducted by Vergara et al. (2022) was able to demonstrate that stress (amongst many other baseline variables) can greatly impact the effect MMT has on mindfulness scores. Thus, it is important to carefully consider baseline factors when completing an MMT study.

6.2 Web-Based MMT Limitations:

While the results of this dissertation project provide evidence of the effectiveness of web-based MMT, it is important to consider its limitations. For example, the duration of the web-based MMT (31 days), in comparison to other MMT programs (e.g., the 8-week mindfulness-based stress reduction program; MBSR) was brief. While our results were able to demonstrate MMT-elicited effects on both the behavioral and neuronal levels despite the training's brevity, the effects observed in this dissertation project may have been strengthened given a longer MMT duration. In fact, previous research has been able to demonstrate that psychological measures of interest could be moderated by the length (i.e., number of hours) of MMT conducted (Khoury et al., 2015; Sedlmeier et al., 2018). To this end, increasing the duration of the MMT could elicit larger effects. Nevertheless, despite the comparatively brief MMT, our training programs demonstrated that even a 31-day MMT could elicit significant behavioral and neuroplastic changes.

In addition, while this dissertation project was successfully able to demonstrate the effectiveness of web-based MMT without any in-person components, it may be important to consider the possible benefits of integrating direct contact with a mindfulness expert to help novice MMT practitioners solidify the fundamental processes involved in MMT, as well as answering any open questions practitioners may have. While some novice MMT-practitioners notice immediate improvements in mental health and well-being, some initial MMT-related challenges can occur. For example, novice MMT practitioners may encounter initial difficulties in focusing their attention, ‘quieting’ their minds, or may even encounter and increase in anxiety levels during the first MMT sessions (Aizik-Reebs et al., 2021; Anālayo, 2019; Britton et al., 2021; Van Gordon et al., 2017). These initial difficulties can be discouraging and may cause novice practitioners to abandon the practice prematurely. Therefore, it may be beneficial to have contact with an MMT expert or coach during the initial MMT sessions to help navigate any potential challenges.

Another limitation to consider is that MMT may not be suitable for those with specific mental health conditions. For example, with regard to eating behavior, MMT may not be suitable for individuals with anorexia nervosa, an eating disorder characterized by a distorted body image and fear of weight gain. MMT’s practice on the focus of bodily sensations and emotions could exacerbate obsessive thoughts about food and body image, potentially reinforcing disordered eating behaviors in anorexia nervosa patients. However, additional research is required to investigate MMT’s specific effects on individual clinical populations.

To this end, it is important to note that MMT should not be utilized as a replacement for professional help. Instead, MMT can be employed as a valuable, additional, component to other therapeutic interventions and treatment mechanisms. Individuals with eating disorders should, therefore, seek professional treatment from a multidisciplinary team to address their unique needs to promote recovery.

Despite these limitations, an open and informed approach to MMT can still yield positive results for many individuals. Seeking guidance from experienced instructors or scientifically backed programs, along with maintaining realistic expectations, can help individuals navigate these limitations. The successful navigation of these limitations will emphasize the benefits of MMT including improved well-being, stress reduction, in addition to an improved relationship with food.

6.3 The History and Cultural Tradition of Mindfulness Meditation

It is also important to be aware of and respect the cultural traditions of mindfulness meditation and its basis from the teachings and philosophies of Buddhism. Mindfulness meditation, or "vipassana," has been an integral part of Buddhist practice for over two millennia, serving as a cornerstone for spiritual growth and self-awareness. Acknowledging MMT's cultural origins can not only enrich the practice of MMT but can also help to ensure sensitivity and respect towards the communities who have preserved and practiced meditation for generations.

6.4 Limitations of Functional MRI

This dissertation project must also acknowledge the methodological limitations of functional MRI. One of the more prominent limitations is its relationship between spatial and temporal resolution. In an effort to capture brain activity over time, neuroimaging researchers are required to weigh the spatial resolution cost of acquiring images more quickly, or – alternatively- the temporal resolution cost of acquiring images with higher millimeter resolution. However, within the scope of this study, the scanning parameters were adjusted to account for the study design (i.e., event-related in Project 1 and block design in Project 3) to optimize both spatial as well as temporal resolution.

Another factor to consider in fMRI research is that the technique is, in and of itself, an indirect measure. The method presupposes that changes in BOLD signal are related to changes in neuronal firing rates. Researchers have, however, investigated the biological basis of the BOLD signal and have gained a foundational understanding pertaining to the complex interplay between the local blood flow, blood volume, as well as the metabolic rate of oxygen to support BOLD imaging as an indirect measure of brain activity (Logothetis & Wandell, 2004).

Another limitation frequently encountered in neuroimaging research is the small sample size. However, given that in Projects 1 and 3, behavioral measures could be correlated with the changes observed on the neuronal level, the reliability of these results is increased.

In addition, regarding Projects 1 and 3; given the nature of the region of interest analysis, the results risk having overlooked other relevant interactions. Further investigation using data-driven methods is required to continue to investigate further interactions.

Despite these limitations, this dissertation project provides valuable insights into how MMT influences brain function, functional organization of the brain, stress reduction, and eating behavior.

6.5 Limitations of ALE

Lastly, this study acknowledges the inherent limitations of the activation likelihood estimation (ALE) model. One of its primary limitations is the inability to control for methodological differences between studies. While efforts were made to extract methodological details from each publication, it is not possible to account for all differences. Technological and methodological advancements over the publication period for data extraction may have influenced reported activations. However, many measures were taken and implemented to ensure the robust statistical outputs of MA maps (Eickhoff et al., 2009).

7.0 Clinical Relevance

The results of this dissertation project have noteworthy clinical relevance in two research domains. Not only do the results provide insight into the neural mechanisms of stress reduction, eating behavior, and MMT, but it is also able to provide insight into the neural processing of the olfactory cortex, which has gained new relevance due to the onset and long-term effects of the SAR-CoV-2 pandemic.

7.1 MMT & Future Clinical Applications

Not only were the results of this dissertation project able to demonstrate the effectiveness of web-based MMT programs, but the results were also able to contribute to the literature on MMT as a mechanism for stress reduction and its relevance for improving well-being, perceived stress, anxiety, attention, as well as stress-eating behavior. While these studies were conducted with healthy participants, future research projects should consider evaluating the effectiveness of web-based MMT in clinical populations. Due to the feasibility and ease with which web-based MMT programs can be administered, in addition to considering the smaller funding budgets required to run web-based MMT studies, these factors could expedite the ability to conduct subsequent studies on clinical populations in comparison with in-person MMT programs.

If web-based MMTs are effective in clinical populations, they could additionally help to alleviate some of the current strains placed upon the healthcare systems worldwide. To this end, given the diverse results observed in this dissertation project, web-based MMT should be studied on a variety of clinical populations, including individuals with anxiety or depressive disorder, attention deficit disorder, or individuals suffering from eating disorders.

Additionally, if future studies have access to neuroimaging techniques, the acquisition of structural and functional MRI data would only continue to contribute to the understanding of how MMT implicates brain structure and function and could provide essential information on neuronal differences in clinical populations.

7.2 Statistically Locating the Olfactory Cortex in times of SARS–CoV–2

Through the completion of an extensive meta-analysis, this project was able to successfully identify the neural processing nodes of olfactory stimulation. These activation likelihood estimation maps were not only relevant for the subsequent neuroimaging analyses on the food-related mindfulness training task, but the results of this meta-analysis gained relevance through the onset of the SARS-CoV-2 pandemic as it contributed to the understanding of the olfactory system.

8.0 iOS App Development Project

The majority of this dissertation project was completed during the SARS-CoV-19 pandemic, which brought with it a series of logistical and practical challenges. Having completed the first few months of data acquisition prior to March 2020, our pilot data could already demonstrate the positive effects of MMT on stress-eating behavior.

While Project 3 recruited over 600 individuals to participate, the study had very strict inclusion criteria, rendering many volunteers ineligible to participate in the food-related MMT program. However, upon feeling the effects of isolation and uncertainty brought upon by the pandemic, in addition to the subjective increase in stress-eating and snacking tendencies (due in part to the newfound proximity to the refrigerator and snack cabinets), it was presumed that many individuals, especially those who volunteered to participate in the study, felt similarly. The food-related MMT program was therefore sent to all individuals who were ineligible to participate in the study in hopes of helping to alleviate stress as well as stress-related overeating tendencies elicited by the uncertainty and isolation of the pandemic.

Upon receiving many emails expressing gratitude from those who participated in the food-related MMT, I contacted Martin Lurz from the Technical University Munich's Department of Informatics given his experience working on e-Health and e-Learning platforms to help me initiate the development of a platform to make the MMT more readily available. Consequently, over the past 3 years, together with several informatics master's students completing their interdisciplinary projects (Mathias Quintero, Clemens Ruck, Onur Cakmak, Laura Drossel, Nathalie Pett, Henning Hontheim, Michael Schlicker, Max Obermeier, Bayram Ahmadov, Hans Santoso, Milen Vitanov, Anna Darii, and Tohid Ajdari), an iOS application was developed.

Figure 2 depicts a screenshot of the application page dedicated to tracking the rewards and milestones of the MMT practitioners (featuring a meditating broccoli ☺).

9.0 Conclusion & Future Directions

In conclusion, the three projects included in this dissertation provide valuable insights into the effects of mindfulness training on various aspects of mental health, cognitive function, and eating behavior. Not only do the results of this dissertation provide evidence for the positive effects of MMT on psychological well-being, cognitive performance, and eating behavior, but the behavioral results are supported by observed changes in neural structure and function.

Given these results, the web-based MMT should be considered for preventative as well as therapeutic application in clinical populations.

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Not only do neuroimaging researchers learn, through their experiments, that the brain is a remarkably malleable organ susceptible to undergoing neuroplastic changes, ready to adapt to all things (stimuli, tasks, etc.) thrown its way, but I was personally able to experience the sheer magnitude of the brain’s resilience and adaptability. Given these experiences, I am absolutely fascinated by our brains.

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Publication List

Published:

1. Torske, A., Koch, K., Eickhoff, S., & Freiherr, J. (2022). Localizing the human brain response to olfactory stimulation: A meta-analytic approach. *Neuroscience & Biobehavioral Reviews*, *134*, 104512.

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3. Bremer, B., Wu, Q., Mora Álvarez, M. G., Hölzel, B. K., Wilhelm, M., Hell, E., Tavacioglu, E. E., Torske, A., & Koch, K. (2022). Mindfulness meditation increases default mode, salience, and central executive network connectivity. *Scientific Reports*, *12*(1).

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In Progress:

5. Torske, A., Bremer, B., Hölzel, B.K. Mazca, A., Koch, K.
   Mind*ful*ness Training Reduces Mind*less* Eating Behavior:
   The effects of a food-related mindfulness training on stress-eating and brain function.

6. Torske, A., Lu, A., Denninger, J., Hoge, E., Macklin, E., Lazar, S.
   Modality Matters: The Differing Mechanisms Underlying Mind-Body Stress Reduction

7. Torske, A., Schicker, D., Freiherr, J., Koch, K.
   Mindfulness Meditation Heightens Sensory Awareness

Contribution Description:

1. The contribution to Paper 1 was as follows: study conception and design: AT, KK, JF; data collection: AT; analysis and interpretation of results: AT, SE, KK, JF; draft manuscript preparation: AT, JF. All authors reviewed the results and approved the final version of the manuscript.

2. The contribution to Paper 2 was as follows: study conception and design: MGMA, BB, BKH, MW. KK; data collection: MGMA, BB, MW, EH, AT, EET; analysis and interpretation of results: MGMA, AT, KK; draft manuscript preparation: MGMA, AT. All authors reviewed the results and approved the current version of the manuscript.

3. The contribution to Paper 3 was as follows: study conception and design: MGMA, BB, BKH, MW. KK; data collection: MGMA, BB, MW, EH, AT, EET; analysis and interpretation of results: BB, MGMA, AT, KK; draft manuscript preparation: BB, KK, AT. All authors reviewed the results and approved the final version of the manuscript.

4. The contribution to Paper 4 was as follows: study conception and design: JF, RL, AT; data collection: AT; analysis and interpretation of results: RL, JF; draft manuscript preparation: RL, JF. All authors reviewed the results and approved the final version of the manuscript.

5. The contribution to Paper 5 was as follows: study conception and design: AT, KK; data collection: AT; analysis and interpretation of results: AT, BB; draft manuscript preparation: AT, BB. All authors reviewed the results and approved the current version of the manuscript.

6. The contribution to Paper 6 was as follows: study conception and design: SL, JD, EH, EM; data collection: SL, JD, EH, EM; analysis and interpretation of results: AT, SL, JD, EM; draft manuscript preparation: AT. All authors reviewed the results and approved the current version of the manuscript.

7. The contribution to Paper 7 was as follows: study conception and design: AT, JF, KK; data collection: AT; analysis and interpretation of results: DS; draft manuscript preparation: AT. All authors reviewed the results and approved the current version of the manuscript.