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Various epigenetic modulations of genetic expression in the strive against stress

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Dedications

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Dedications

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Abstract

It is confirmed that stress causes epigenetic changes that cause the appearance of several diseases. It seems that the treatment of these epigenetic modifications does not necessarily do this through medical and pharmaceutical drugs as we have always known, but can do this through the mind body interventions (MBI's).

Today people are looking at this more and more, that it is unlikely that such interventions can bring about changes at the molecular and physical level. Is this the true concept or not?

Now through bibliographic research, it has been shown that the mind body interventions can restore an epigenetic disorder.

The interventions between the psychic and the somatic (psychosomatic), induce not only psychological changes, such as the mitigation of depression, anxiety and stress, but also physiological changes such as parasympathetic activation, lower cortisol secretion, reduced inflammation and delayed aging, and various other vital processes, all of which are a risk factors for multiple diseases. The narrow link between the mind and the physical body in a state of mutual influence installs either a pathology or a recovery from a disorder being the origin of this disease. This would thus restore epigenetic disorders by modulating the expression of the genes involved. For this we studied 23 articles, which gave us several results regarding multiple types of MBI's such as meditation, yoga, Tai Chi, Qigong, MBSR, mindfulness and relaxation, which had an impact on various diseases. The Type 2 diabetes as a detailed example, showed that these practices could decrease blood glucose.

So indeed, today we can say that such means of meditation can establish a balance between the mind and the physical body, can re-establish an epigenetic disorder and allow to live protected from stress for a life full of health and good quality.

Keywords : Stress, epigenetics, genes, mind-body interventions, meditation, disease.

Résumé

Il est confirmé que le stress cause des modifications épigénétique qui provoque l'apparition de plusieurs pathologies. Il parait que le traitement de ces modifications épigénétiques ne se fait pas forcément à travers des médicaments comme on l'a toujours connue, mais peut se faire à travers des interventions entre le mental et le corps physique.

Aujourd'hui les gens se penchent sur ça de plus en plus, qu'il est invraisemblable que de tels interventions peuvent apporter des changements au niveau moléculaire et physique. Serait-il ce concept vrai ou pas ?

Maintenant à travers une recherche bibliographique, on est arrivé a démontré que des moyens comme les interventions entre le mental et le corps physique peuvent rétablir un désordre épigénétique.

Les interventions entre le psychique et le somatique (psychosomatique), induisent non seulement des changements psychologiques, tels que l'atténuation de la dépression, de l'anxiété et du stress, mais aussi des changements physiologiques tels que l'activation parasympathique, une sécrétion de cortisol plus faible, une inflammation réduite et un retard du vieillissement et diverses autres processus vitaux, qui sont tous des facteurs de risque de maladies multiples. Le lien étroit entre le mental et le physique dans un état d'influence mutuelle installe soit une pathologie soit un rétablissement d'un désordre étant à l'origine de cette maladie. Ça parviendrait donc à restaurer les désordres épigénétiques en modulant l'expression des gènes impliqués. Pour cela nous avons étudier 23 articles, ce qui nous a valu plusieurs résultats concernant multiples types de méditations, yoga, Tai Chi, Qigong, MBSR, la pleine conscience et la relaxation, qui ont eu un impact sur de diverses pathologies, le diabète de type 2 pris comme exemple détaillé, a montré que ces pratiques pourraient diminuer le glucose du sang.

Donc en effet aujourd'hui on peut dire que de tels moyens de méditations peuvent mettre en place un équilibre entre le mental et le physique, peuvent rétablir un désordre épigénétique et permettent de vivre en protégé du stress pour une vie pleine de santé et de bonne qualité.

Mots-clés : Stress, épigénétique, gènes, interventions du corps-mental, méditation, maladie.

ملخص

تم التأكيد على أن الإجهاد يسبب تغيرات وراثية تسبب ظهور العديد من الأمراض. يبدو أن علاج هذه التعديلات اللاجينية لا يتم بالضرورة من خلال الأدوية كما كان معروفًا دائمًا، ولكن يمكن القيام به من خلال التدخلات بين العقل والجسد.

ينظر الناس اليوم إلى هذا أكثر فأكثر، وأنه من غير المرجح أن تؤدي مثل هذه التدخلات إلى تغييرات على المستوى الجزيئي والفيزيائي. هل هذا المفهوم حقيقي أم لا؟

الآن من خلال البحث الببليوغرافي، ثبت أن مثل التدخلات بين العقل والجسم المادي يمكن أن تعيد الاضطراب اللاجيني.

لا تؤدي التدخلات بين الحالة النفسية والجسدية (النفسية الجسدية) إلى تغييرات نفسية فقط، مثل التخفيف من الاكتئاب والقلق والتوتر، ولكن أيضًا التغيرات الفسيولوجية مثل التنشيط السمبتاوي، وانخفاض إفراز الكورتيزول، وانخفاض الالتهاب وتأخر الشيخوخة، والعديد من العمليات الحيوية الأخرى، وكلها عوامل خطر لأمراض متعددة. العلاقة الوثيقة بين العقل والجسد في حالة التأثير المتبادل تثبت إما علم الأمراض أو التعافي من الاضطراب في أصل هذا المرض. لذلك من شأنه استعادة الاضطرابات اللاجينية عن طريق تعديل التعبير عن الجينات المعنية. لهذا قمنا بدراسة 23 مقالة، والتي أعطتنا العديد من النتائج فيما يتعلق بأنواع متعددة من التأملات، اليوجا، تاي تشي، تشيغونغ، MBSR، اليقظة والاسترخاء، والتي كان لها تأثير على مختلف الأمراض، أظهر مرض السكري من النوع 2 كمثال مفصل أن هذه الممارسات يمكن أن تقلل من نسبة السكر في الدم.

لذلك يمكننا اليوم أن نقول إن مثل هذه الوسائل للتأمل يمكن أن تؤسس توازنًا بين العقل والجسم، ويمكن أن تعيد إحداث اضطراب وراثي وتسمح بالعيش محميًا من الإجهاد لحياة مليئة بالصحةوالجودةالجيدة.

الكلمات الرئيسية: الإجهاد، التخلق علم، الجينات، تدخلات جسم العقل، التأمل، المرض.

Table of Contents

List of Abbreviations and Acronyms

Ac adn =Acyl Coenzyme A Dehydrogenase

Ap =Activation Protein

Apo b =Apolipoprotein B

Apoc c= A Polyprotein C

BMI =Body Mass Index

BP=blood pressure

Cbt =Cognitive Behavior Therapy

Cct= Non-Randomized Controlled Trial

CD2=cluster of differentiation 2

CLDF 11a= C_Type Lecture Domain Family Member A

CNS = Central Nervous system

COX 2 =Cyclooxygenase 2

CPT1a= Carnitine Palmitoyl Transferase 1a

CR =Caloric Restriction

CREB= Camp Response Element Binding Protein

Crp= C Reactive Protein

Cs =Cross Sectional

DNAm= Dna Methylation

DSME= Diabetes Self-Management Education

EGRP= Early Growth Response Protein

ETIF1b= Eukaryotic Translation Initiation Factor 1b

ESR =Erythrocyte Sedimentation Rate

FBG= Fasting Blood Glucose

FENO= Fractional Exhaled Nitric Oxide

GR= Glucocorticoid Receptor

GSEA= Gene Set Enrichment Analysis

HbA1c= Hemoglobin a1c

HDL c= Hight Density Lipoprotein Cholesterol

HPA =Hypothalamus Pituitary Adrenal

Hrh 1= Histamine Receptor h1

IEAA =Intrinsic Epigenetic Age Acceleration

IL= Interleukin

INS= Insulin Protein

IRF =Interferon Regulatory Factor

Klf15= Kruppel Like Factor 15

L= Longitudinal

LDL c= Low Density Lipoprotein Cholesterol

LKM= Loving Kindness Meditation

MAAS= Mindful Attention Awareness Scale

MaFK= Musculoaponeurotic Fibrosarcoma Oncogene Homolog K

MBCT =Mindfulness Based Cognitive Therapy

MBI's= Mind Body Interventions

MBSR= Mindfulness-Based Stress Reduction

MDD =Major Depressive Disorder

miRNA= microRNA, a small non-coding RNA molecule that can interfere with the expression of a gene after it is transcribed

mRNA= Messenger RNA, a large family of RNAs that transport genetic infomation from DNA to ribosomes

NF-κB= Nuclear Factor Kappa B

NCBP= Nuclear Cap Binding Protein

NCoR= Nuclear Receptor Co-repressor

NFATC2 =Nuclear Factor Of Activated T Cells 2

Nr= Not Reported

NFE2L2= Nuclear Factor Erythroid 2 Related Factor 2

PBMC= Peripheral Blood Mononuclear Cell

PPBG= Post Prandial Blood Glucose

PTSD =Post-Traumatic Stress Disorder

RCT =Randomized Controlled Trial

Rna Seq= Rna Sequencing

RR = Rapid Response

Rt PCR = Real Time Polymerase Chain Reaction

RTL =Relative Telomere Length

Serpin b9= Serine proteinase inhibitor B9

SNS= Sympathetic Nervous System

TA= Telomer Activity

TC =Total Cholesterol

Telis =Transcription Element Listening System

TG= Triglyceride

TL =Telomere Length

TLR =Toll Like Receptor

TM= Transcendental Meditation

TNF= Tumor Necrosis Factor

TNFR= Tumor Necrosis Factor Receptor

TrG =Telomere Related Gene

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Introduction

Introduction

Over several years, evidence has grown that links stress to huge number of illnesses and diseases, both acute and chronic stress can induce genetic and epigenetic changes although, mathematically, they are more likely to occur during chronic stress. Thus, adaptive pressure due to chronic stress could lead to the evolution of abnormal cell states that contribute to disease. But there's a way to prevent and heal from many health problems, using the same process in a reversed way, which is through mind body interventions (MBI's) and multiple types of meditation.

Over the past 40 years, meditation and related mind–body practices have attracted progressively greater attention from the scientific and health-care community. This has led to a growing body of evidence describing how these practices might affect mental and physical functions.

Benefits and adverse effects of MBIs were reported in surveys from differentcountries. MBIs are using by Physical therapists with individuals with varioushealth conditions, in order to reduce certain diseases, particularly related tostress and to improve the physical and mental health.

For decades, MBIs have been the subject of numerous studies. 10 articles (2reviews and 8 original articles) were synthesized in this study to demonstratethe effect of MBIs on gene expression, the different types of MBIs and itfunction and the benefits and adverse effects of MBIs.

This study aims to determine the effects that MBI has on health from themental to the molecular level. It aims to document the functional outcomesassociated with the participation of MBIs and provide the rationale for MBIs asa complementary, integrated, reimbursable health approach.

CHAPTER ONE
BIBLIOGRAPHY

I.1. The Stress

The term “stress” has become common vocabulary in Western culture and has been associated with a set of negative psychological conditions. Many studies have linked stress to common health problems include: hypertension, heart disease, substance abuse, anxiety, depression, gastrointestinal disorders, cancer, headaches and back pain ...etc (S. Cohen, Janicki-Deverts, & Miller, 2007; Conti, Maccauro, &Fulcheri, 2011; Spruill, 2010; Yudkin, Kumari, Humphries, & Mohamed-Ali, 2000). However, their definitions vary depending on different contexts and different people.

Despite the ongoing fluxes in defining what psychological stress is, its physiological impact can be characterized by short-term and sustained long-term changes. The short-term response or acute response has popularly been labeled the “fight or flight response” and is beneficial in a critical or life-threatening situation (Georgina Russell ,& Stafford Lightman, 2019). When these short-term stress events become frequent or prolonged, they result in chronic stress which over time may contribute negatively to a person's mental and physical health (Agnese Mariotti, 2015).

I.2. The Stress Response on a Genetic Level in General

Over several years, evidence has grown that links chronic cell stress to diseases, which include cancer, cardiovascular disease, diabetes and neurodegenerative disorders (Beckman JA, Creager MA, & Libby P, 2002; Hotamisligil GS, 2010; Visconti R, &Grieco D, 2010, Zawia NH, Lahiri DK, & Cardozo-Pelaez F, 2009). There are many possible explanations for how cell stress contributes to disease; for example, direct cytotoxicity, mutagenesis, or disturbance of intracellular signalling cascades. In the course of development and in adults, chronic stress may also alter the normal balance of cell maturation and division in cell renewal systems, and there is new evidence of thisalterations might be linked to disease.

Cell renewal systems, in a broad sense, are composed of self-renewing stem cells and more committed progenitor cells that give rise to mature cells. According to the system, in their basal state, self-healing cells may divide quickly (as in the intestinal epithelium) or rarely divide (as in muscles and neurons). Stress can trigger a change in the stem cell numbers and rate of division (Rossi DJ, Jamieson CH, & Weissman IL, 2008; Silva H, &Conboy I, 2008; Chambers SM, et al, 2007). During acute stress, such as a transient

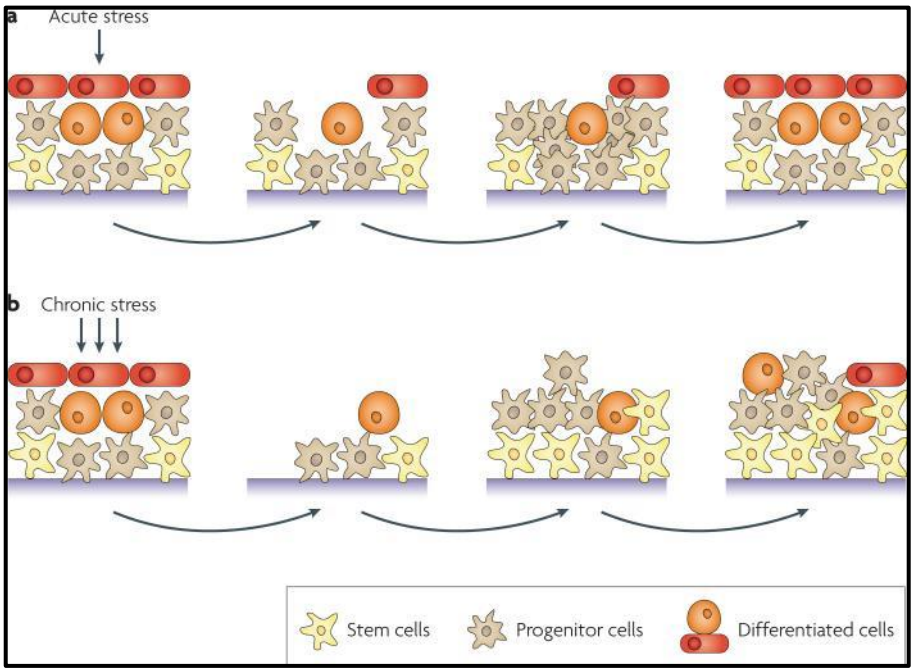

Figure1:*The effect of stress on cell renewal systems (Johnstone and Baylin, 2011)*

injury with rapid repair, increased division of the progenitor cells and subsequent differentiation of their offspring are often necessary for tissue homeostasis (FIG. 1a).In contrast, prolonged exposure to stress presents a much more severe challenge for cells in self-renewal systems and to maintain tissue homeostasis., replacement systems may be filtered (Coussens LM et al, 2002) (Figure 1b).. Acute and chronic stress can cause genetic and epigenetic changes, even if, mathematically, they are more likely to occur during chronic stress. As a result, adaptive pressure due to chronic stress may lead to abnormal cellular conditions that contribute to the disease.**a |** In an acute stress setting, transient stress might replacement tissue stem cells that harm other types of cells..This may lead to transient mobilization of progenitor cells (beige) to replenish differentiated cells (red and orange) and achieve tissue homeostasis

b |In a context of chronic stress, there is a more pronounced and continuous effect on cell replacement systems with injuries of all cell types, including stem cells (yellow)..Tissue response involves the mobilisation and continual renewal of stem cells and progenitor cells.Genetic and epigenetic changes may alter the condition of these cells, resulting in abnormal tissue homeostasis and susceptibility to diseases like cancer..

A result of chronic stress may be the identification of abnormal cell states that may persist even if exposure is eliminated or decreased.A combination of genetic and/or epigenetic changes generated during the stress period could result in a change in cellular "memory" that helps to stimulate disease pathology.It is known that epigenetic mechanisms play a significant role in normal cellular memory (Bird A, 2002). Chromatin compaction and organization, which can be influenced by DNA methylation, histone variants, histone post-translational modifications and nucleosome remodelling, help to determine the gene expression profiles that define and maintain cell identity (Kouzarides T, 2007; Li B, Carey M, & Workman JL, 2007; Misteli T, 2007; Lister R, et al, 2009; Hawkins RD, et al, 2010). Hence, the chromatin structure should be carefully controlled in auto-renewal cells and differentiated in cell-renewal systems..In fact, specific cell types have been shown to have specific epigenetic characteristics, and stem cells differ considerably from differentiated terminal cells. (Lister R, et al, 2009; Hawkins RD, et al, 2010).

It is important to note that there is now a great deal of evidence that cells involved in several major human pathologies have aberrant patterns of epigenetic changes and, in many cases, these epigenetic patterns can contribute to this.substantially to the disease-causing cellular phenotypes (Esteller M, 2008). In this study, we bring together several examples of diseases in which chronic stress as an epigenetic tool has been implicated. We consider three distinct but potentially concomitant consequences of epigenetic changes that are involved in the disease: abnormal cell proliferation, cell loss and/or dysfunction and cell condition. (FIG. I-2).

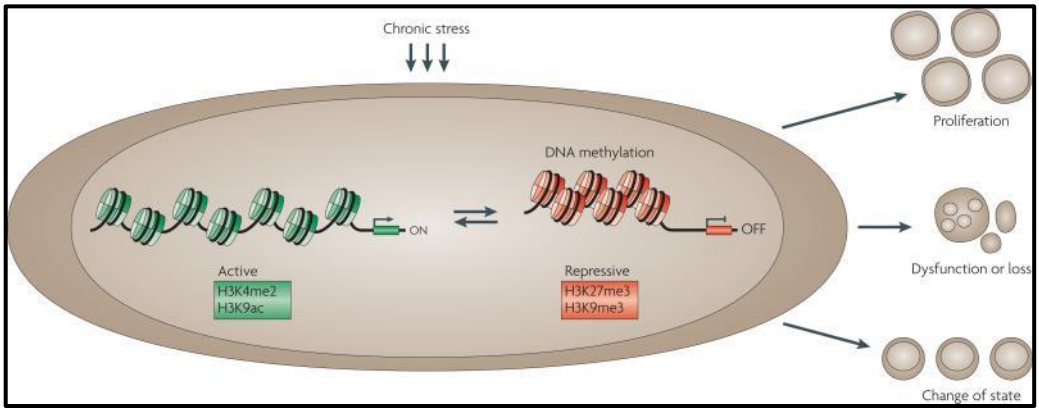

Figure2:*Perturbations caused by chronic stress (Johnstone and Baylin, 2011)*

Chronic stress may result in epigenetic changes. For example, alterations in DNA methylation, histone modifications and nucleosome positioning might occurIn the example below, the modifications cause the genes to become extinct. Epigenetic changes can give rise to hereditary models of altered gene expression that translate into abnormal cellular states: proliferation, dysfunction or loss, or change of state. These changes may contribute to illness, as discussed in the paper. The histone modifications shown here associated with active transcription are histone H3 lysine 4 di-methylation (H3K4me2) and H3 lysine 9 acetylation (H3K9ac); the modifications associated with transcriptional repression are H3 lysine 27 trimethylate (H3K27me3) and H3 lysine 9 tri-methylated (H3K9me3).

These examples lead us to suggest that chronic stress can cause alterations in the chromatin landscape that can drive these cellular outcomes:

Abnormal Cell Proliferation:

- Cancer (including breast, colon, prostate, and lung malignancies)
- Cardiovascular diseases:
    - Arterial hypertension and cardiomyocyte reversion which can lead to cardiac hypertrophy and heart failure (Hang CT, et al, 2010).
    - Atherosclerosis leading to aberrant cell expansion.

Cellular Dysfunction or Loss of Functional Cell Populations

This is a second potential consequence of stress, induced epigenetic changes and may have a role in multiple diseases (Villeneuve LM, & Natarajan R, 2010), such as:

- Neurological disorders (Autism Spectrum Disorders (ASDs) (Nguyen A, et al 2010), alzheimer's disease (AD), Parkinson’s disease (Bonda DJ, et al, 2010).
- Diabetes both type 1 and type 2 (Villeneuve LM, Natarajan R, 2010; Schanen NC, 2006).

Changes in Cell State

A third cellular stress response that could be mediated through changes in epigenetic states is the alteration of cellular states in the context of cell renewal. Epigenetic control is the key factor that normally regulates changes in cellular becoming in adult cell development and renewal systems.For example, DNA methylation changes can be important, as indicated by reports that depleting the DNA methylation-catalysingenzyme

DNMT1 in normal mouse hematopoietic and human epithelial cells blocks self renewal and appropriate cell maturation, resulting in depletion of progenitor cells (Broske AM, et al, 2009; Sen GL, 2010). These changes can occur in normal cells or by reprogramming non-renewing cells. We suggest that the chronic stress of cell renewal systems leads to the commutation of cellular destinies, and that this process is epigenetic and can play a profound rolein the pathology of multiple diseases, for example cancer and diabetes.

Now that we have seen what stress is and how does he affect our health and how many health problems and diseases are caused by stress, scientists had asked themselves the following question which is, what will happen if we reverse the process of getting stressed by involving the emotion of relaxation and inner silence to get into an inner peace state?

So, they suggested multiple techniques for stress relief and a constant peaceful and relaxed state. In this thesis we have selected some mind body interventions (MBI's) techniques to study and see further their impact on the genetic landscape and the overall health.

Those MBI's are commonly called by one well known term which is "meditation", so we will get to know what meditation is, but we will also get to know the definition of the different appellations and types of meditation which we would better describe as mind body interventions (MBI's).

I.3. Introducing Epigenetics

Over the last decade or so, the field of epigenetics has emerged as a new and powerful way to understand the biological mechanisms that regulate health and disease. Epigenetics is a molecular biology discipline that differs from genetics because, rather than focusing on the identification of genes that lead to the expression of a certain phenotype or disease risk, or the inheritance of such genes, it examines the mechanisms that regulate the expression of genes. Epigenetics is thus predicated on a new understanding of how the genome operates – as a dynamic system that can act in very short time periods to activate or deactivate a gene and hence its ability to support the production of the proteins that it codes for (Allis, Jenuwein, &Reinberg, 2007).

In other words, a single genome can have multiple, different epigenetic and hence phenotypic destinies depending on which environmental factors might act on it at crucial time points in the organism’s development. This is why the new field of epigenetics is seen

in many ways to contradict the traditional view of the genome – that our genes are locked into an unchangeable pathway of development after they are produced. In traditional genetics, DNA replication and gene expression are controlled by elements such as promoters, enhancers or binding sites for repressor proteins which are present or absent in the DNA sequence itself. In contrast, epigenetic mechanisms modify the conformation of the DNA and the accessibility of other factors to DNA without altering the DNA sequence. It thus refers to a level of control external to the DNA which modifies how the DNA is read rather than to alteration of the DNA sequence itself. This external control allows for genes to be effectively switched between the "on" or active state and the "off" or inactive state, both of which can occur without causing changes to the DNA sequence (Jaenisch & Bird, 2003). This phenomenon adds an extra explanation as to why although all cells contain the same DNA, they can display different phenotypes. For example, our body contains a myriad of cells ranging from skin cells to liver cells all of which have the same DNA present. The phenotype displayed is clearly attributed to epigenetic regulation of the DNA. Another differentiating factor of epigenetics is that these gene expression changes can be inherited by the next generation (García-Giménez, 2015; Heard &Martienssen, 2014). Epigenetics therefore offers an understanding of the biological mechanisms that underlie virtually every aspect of biological function.

Most importantly, epigenetic tests have now reached a level of breadth, sophistication and affordability that allows broad insights into the full spectrum of physiological systems that might become more or less active over even short time periods in response to a given stimulus.

Previously, investigations into the biology of meditation were restricted to relatively narrow avenues of enquiry, the commonest being:

- Peripheral physiological measures of autonomic activity such as: blood pressure, heart rate, skin temperature, galvanic skin resistance and more recently heart rate variability (Chatterjee, Ray, Panjwani, Thakur, &Anand, 2012; Chung, Brooks, Rai, Balk, & Rai, 2012; Yunati, Deshp, &Yuwanate, 2014)
- Neuroendocrine factors such as circulating stress hormones (catecholamines, cortisol), endorphins, oxytocin, ACTH and aldosterone (Infante et al., 1998; Turakitwanakan, Mekseepralard, &Busarakumtragul, 2013)

- Central nervous system assessment methods aimed at assessing brain activity such as electroencephalogram, functional magnetic resonance imaging, positron emission tomography and magnetoencephalography (Aftanas & Golocheikine, 2001; Hernandez et al., 2015)

I.3.1. The Biological Mechanisms of Epigenetic Regulation

The mechanisms by which epigenetic changes occur include (but are not limited to) three main processes:

1. DNA methylation (Smith & Meissner, 2013)
2. Histone modification/chromatin remodelling (Bannister &Kouzarides, 2011)
3. RNA interactions. (Holoch & Moazed, 2015)

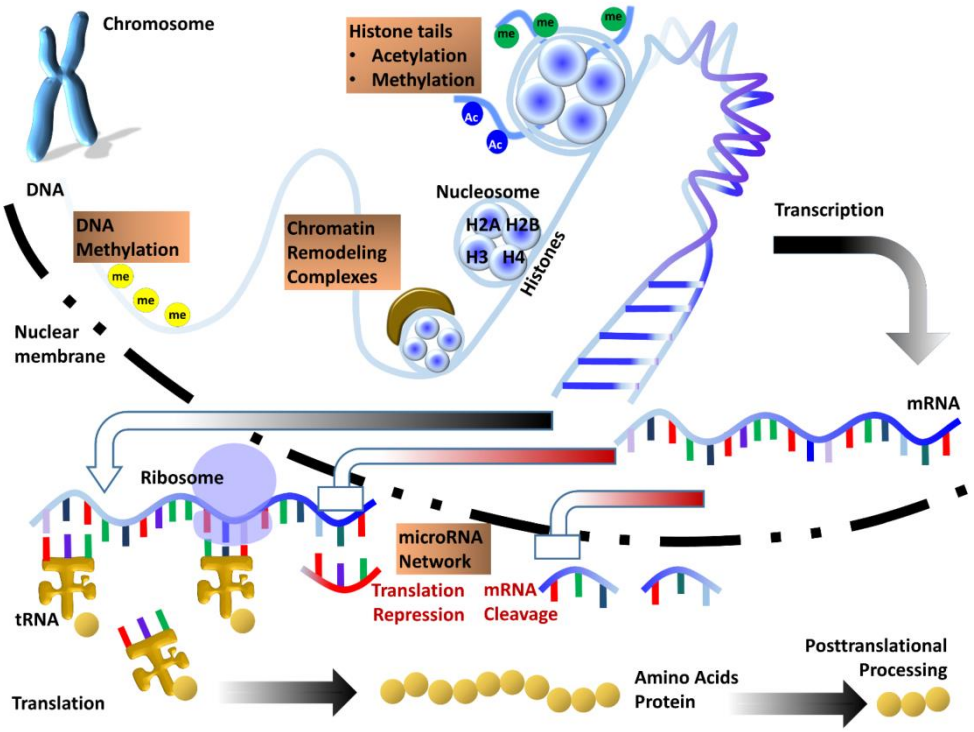

Figure3: *Sketch illustrating the multi-layered control of gene expression by various epigenetic processes(Gopinathan G, Diekwisch TGH,2022). DNA is directly chemically modified by the addition or elimination of methyl groups to cytosine bases. Epigenetic processes that regulate gene expression at higher levels of DNA compaction include histone tail modifications and the control of chromatin accessibility by ATP chromatin-dependent remodeling complexes. Once transcribed, mRNAs may be further regulated by the microRNA network, which provides an extra layer of epigenetic control of gene*

expression. Together, those epigenetic mechanisms work together to help refine gene expression within the cell.

I.3.2. Methylation

The most well-known epigenetic modification is DNA methylation which results in the inhibition of transcription of the gene involved. Methylation occurs exclusively on the dinucleotide sequence which is a link between the base cytosine and the base guanine via a phosphate bond (also known as CpG). It has been noted that the majority of CpGs are methylated and those CpGs which are not methylated are usually clustered together to form CpG islands. Gene expression requires the transcription machinery to be able to easily access the gene promoter region (part of the sequence that is essential in that specific gene‟s transcription). By methylating these promoter regions, it can directly obstruct the transcriptional machinery resulting in the lack of a functional gene product (Lim & Maher, 2010; Razin & Kantor, 2005).

I.3.3. Histone Modification

In the cell nucleus DNA is wrapped around histone proteins to form units called nucleosomes. There are 5 families of histone proteins, H2A, H2B, H3, H4 (core histones) and H1/H5 (linker histones). Each nucleosome is composed of DNA wrapped around 8 core histone proteins which are linked to other nucleosomes via linker histones and linker DNA. Histone modifications affect the way DNA is wrapped around them which in turn leads to the different expression of different genes. Histone acetylation and methylation are two methods by which histones can be modified (Rice & Allis, 2001). Both these processes are reversible. Histone acetylation occurs on lysine residues on the histones and is catalysed by histone acetyltransferases. This acetylation neutralises the positive charge on the lysine residue thereby reducing affinity between the histones and DNA allowing for the transcriptional machinery to gain access to the DNA (up regulation of DNA transcription). The opposite occurs with the assistance of histone deacytelases (HDACs), causing the DNA and the lysine to gain affinity thereby disrupting gene expression. Histone methylation involves the methylation of the lysine residue on the histones. However, the methylation of different lysines can result in either suppression or expression of the genes, as compared to DNA methylation which only causes gene suppression. Methylation of the

lysine can also be de-methylated by the catalyst lysine demethylase (Cheung & Lau, 2005; Imhof, 2006).

I.3.4. Chromatin Remodeling

This occurs via protein complexes called chromatin remodeling complexes. They use the energy of ATP hydrolysis to change the state of the chromatin via the manipulation of the nucleosomes that the chromatin is wrapped around (Clapier& Cairns, 2009). It is also apparent that chromatin remodeling machinery works in tandem with histone modification enzymes and that both processes are essential for DNA methylation and de-methylation. Similar to histone modification enzymes, there are 4 different classes of remodeling complexes all of which share some basic properties: a higher affinity for the nucleosome than the DNA itself; domains which are able to recognise covalent histone modifications; a region for breaking histone- DNA contacts, domains/proteins that regulate the ATPase domain; domains/proteins required for interaction with chromatin or transcription factors. Although they all have these properties in common, they also have distinctive properties which differ in the composition of the complex subunits and the way they actually interact with the nucleosomes (Geiman& Robertson, 2002).

I.3.5. Non-Coding RNAs

Non-coding RNA (ncRNA) molecules are transcribed from DNA that is not translated into proteins but rather plays a role in the regulation of gene expression via interactions with histones, the DNA and gene silencing. The ncRNAs are divided up into short ncRNA and long ncRNAs, with the short ncRNAs being further divided into microRNAs (miRNA), short interfering RNAs (siRNAs) and piwi-interacting RNAs (piRNAs). MiRNAs bind and either degrade, cleave or block translocation of specific RNA transcripts to regulate the expression of the messenger RNA‟s target. In addition to the functions of miRNA, siRNA is able to induce methylation and chromatin condensation by binding to a RNA-induced transcriptional silencing complex. Finally,piRNAs are transcribed and then bind to PIWI proteins resulting in epigenetic regulation and transposon control (a sequence of DNA that can change its position within the genome) (Esquela-Kerscher& Slack, 2006; Tollefsbol, 2014).

I.3.6. Psychosocial Genomics

In last decade, it has become well established that not only physical changes in our environment but also psychological, and possibly even social and cultural changes can lead to alterations in gene expression (Provencal & Binder, 2015). Gene expression changes associated with the mind–body interaction, are now encompassed by a field called "psychosocial genomics" (Rossi, 2002).

One example of psychosocial genomics occurs during pregnancy (Dipali et al, 2019). Over the past decade there has been mounting evidence that changes in the environment during pregnancy can influence the baby in utero via epigenetic mechanisms (Pathik D et al., 2009). This has become known as the paradigm of the "developmental causes of health and disease" (Izzuddin et al, 2018), the paradigm covers a number of themes including:

- The influence of diet during pregnancy and how this may affect the likelihood of the baby becoming obese during adulthood (Luseadra McKerracher et al, 2019).
- The consequences of mismatch between prenatal and postnatal environments and how this can lead to chronic disease later in life (Izzuddin et al, 2018).
- Psychobiological effects of stress during pregnancy on the development of the fetus and later outcomes (Kieran J O'Donnell & Michael J Meaney, 2017).

The effects of stress on prenatal development have been well documented with effects which have been observed to last into infancy, childhood, adolescence and even adulthood (Sonja Entringer, Claudia Buss, and Pathik D. Wadhwa, 2015). The effects have included:

- Impaired parts of memory and learning such as object recognition and spatial memory (prenatal stress induces spatial memory deficits and epigenetic changes in the hippocampus indicative of heterochromatin formation and reduced gene expression)
- Increased risk of neurological and psychiatric disorders (stress-induced perinatal and transgenerational epigenetic programming of brain development and mental health)
- Reduction in birth weight and subsequently increasing the likelihood of disorders of cardiovascular function, glucose homeostasis, hypothalamic– pituitary–adrenal (hpa) axis activity and anxiety-related behaviours in adulthood (prenatal stress, glucocorticoids and the programming of adult disease).

This highlights the idea that stress during pregnancy can induce long lasting epigenetic changes in the fetus which result in mental and physical health issues that may last well into adulthood. On the other hand, epigenetic studies focusing on adults have established that stress, post-traumatic stress disorder and depression can alter the expression levels of stress related genes (Cole, 2010). Therefore, it is reasonable to expect that meditation might also alter expression of genes that are implicated in stress.

The first study aiming to elucidate the effects of meditation on gene expression was done in 2005 by Li et al. (Q. Z. Li et al., 2005). Using a cross-sectional study design, the results suggested that genomic profiles changed in the practitioners of Falun Gong (an ancient Chinese practice of meditation). Since then, other studies on "epigenetic meditation" have produced equally intriguing results. These are described in the literature review.

I.4. The Meditation

Despite its origins, the definition of meditation appears to vary between authors, historical texts and spiritual philosophies. Numerous attempts have been made to create formal definitions; however, there is still no consensus definition despite 40 years of Western scientific research into meditation. Some examples of attempts to define meditation include:

The authoritative National Centre for Complementary and Alternative Medicine defines it as ***"a conscious mental process that induces a set of integrated physiological changes termed the Relaxation Response"*** (National Center for Complementary and Alternative Medicine, 2004).

Currently in the West, meditation is commonly associated with Buddhism and hence Buddhist ideas about meditation – of which mindfulness is without doubt the most prominent.

However, scholars widely acknowledge that meditation pre-dated Buddhism by thousands of years. There are numerous texts describing meditation and its associated ideas in pre-Buddhist Hindu texts for example, making it obvious that the origins of meditation go as far back as 7000 BC (Feuerstein, 2006; Mascaro, 1965; Srinivasachariar&Sastri, 1946). Amongst these texts is a variety of discussions about meditation and its related philosophies. Within these texts one finds a more ancient idea of meditation that both

predates mindfulness and is conceptually specific and distinct from it, as well as the other more modern concepts of meditation described above.

I.5. Mental Silence

In the Katha Upanishad (thought to be written sometime during the first millennium BC) the meditative experience is described as this notion of the "still mind" is reflected in the even older texts of the Mahabharata mythology (approximately 3000 BC),

This description seems to further clarify the fact that the characteristic feature of meditation can actually be the experience of non-thought while remaining fully alert and conscious., that is, “mental stillness” or “mental silence”. The Sanskrit terminology for this particular condition is nirvicharasamadhi (Patanjali, Prabhavananda& Isherwood, 1991)

The concept of "mental silence" has received little consideration in Western scientific literature, but there is a small but growing amount of research that suggests it is deserving of greater attention. There are a number of unique and specific experiential characteristics of mind silence:

- Present moment awareness
- Positive mood
- Expanded consciousness
- Positive health/wellness in all spheres (bio-psycho-social and spiritual)
- A sense of integration/synergy of faculties
- A sense of cosmic connection and unity
- Trans cognitive/beyond thought
- Specificsomaticsensations/descriptorsthat somehowreflectintuitive knowledge.

I.6. Types of Mind–Body Intervention and their Effects

Mind–body intervention (MBI, also known as mind–body training, mind–body practices, and mind–body therapy) refers to meditation, mindfulness, yoga, qigong, relaxation response and tai chi, that deal with both physical and mental well-being (Wahbeh H, Elsas SM, &Oken BS, 2008) These interventions are performed with the goal of gaining positive influence on overall health by fostering mental serenity, mental care, critical cognition, as well as improving bodily function through respiration and physical motion. MBI may be classified as static methods (sitting meditation), dynamic methods

(moving meditation), and a combination of the two.. Static methods can include mindfulness meditation, transcendental meditation (TM) and relaxation response. Mindfulness meditation is a well-known way to cultivate a state of mindfulness in everyday life (Black, D.S.; Slavich, G.M,2016). TM is a form of silent mantra meditation with one's eyes closed (Wallace, R.K,1970). Relaxation response is a simple, secular version of TM (Benson, H.; Beary, J.F.; Carol, M.P,1974). With respect to content, the static method can be divided into open monitoring meditation (e.g., mindfulness meditation) and targeted attention meditation (e.g., MC, brainwave vibration).

Dynamic MBIs include movement meditations, such as yoga, tai chi, and qigong, which can be considered as a combination of mindfulness intervention and physical activity (Creswell, J.D, 2017). Yoga is a group of physical, mental, and spiritual practices or disciplines, largely consisting of different yogic postures (Feuerstein, G, 2012). Tai chi is a moving meditation involving a series of slow, gentle motions that are patterned on the movements in nature. Qigong is often called the "internal" part of tai chi and is characterized by stationary movements that are repeated several times.

The combined protocols entail a mixture of static meditations and movements. Mindfulness-based stress reduction (MBSR) is an 8-week integrated training consisting of mindfulness meditation, concentrative meditation, breathing exercises and yoga (Kabat-Zinn J, 2003). It blends various techniques and is referred to in the clinical setting as mindful awareness practices (Bower JE et al, 2015), mindfulness-based movement (Robert-McComb JJ et al, 2015), mindfulness-based interventions (Black DS; &Slavich GM 2016), and so on. Brain wave vibration meditation (also known as brain education meditation (BEM)) is a combination of static and dynamic methods that manages health of body and mind based on the following five steps: (1) Brain sensitizing (activating the connection between the body and the brain through various body movements), (2) brain versatilizing (making one's body flexible through yoga, breathing exercises), (3) brain refreshing (brain wave vibration, energy dance), (4) brain integrating (imagery meditation, body scan), and (5) brain mastering (philosophy of enlightenment) (Lee I, 2016; & Lee I, 2009).

MBI has been reported to relieve stress-dependent symptoms of various diseases, including psychological disorders (mood and anxiety disorders), inflammatory diseases, aging, and cancer (Bower JE et al, 2015; Chételat G et al, 2018). The incidence and

progression of diabetes can be affected by stress (Hackett et al, 2016). Therefore, MBI can be beneficial for patients with diabetes for example, and many other diseases.

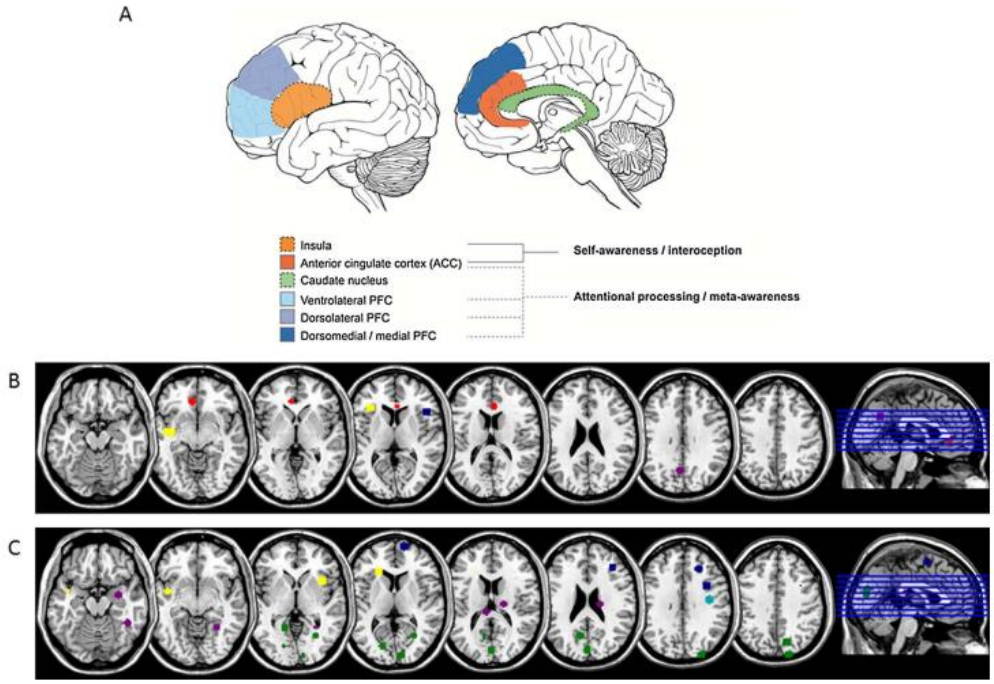

Figure4:An an overview of the regions showing a shift in task-based activity following eight-week manual mindfulness interventions (Young et al, 2017)*. A) Regions are listed in order of most reproducible findings across studies and are colour-coded according to function. Insula (yellow) (Haase et al. 2015; Hölzel et al. 2011; Johnson et al. 2014; Tomasino and Fabbro 2016) and CCA (orange) (Haase et al. 2015 by Johnson et al., 2014)are involved in caring processes, including interoception and conflict detection, respectively, as well as emotional treatment and regulation. The caudate core (green) (Haase et al., 2015; Tomasino and Fabbro, 2016) is included in the reward circuits.The areas shown in blue are prefrontal cortical zones where we have not found strong evidence of changes in activity as a result of 8 weeks of manual mindfulness interventions. but have been related to changes in mindfulness in individual studies. (ventrolateral PFC (Hölzel et al., 2011), dorsomedial PFC (Goldin et al., 2012), medial PFC (Ives-Deliperi et al., 2013), dorsolateral PFC (Haase et al., 2015). B & C) Tranches representing areas of significant change in activation following mindfulness interventions showing the results of: (B) group-by-time interactions and (C) effects within subjects.ROIs are represented by 6 mm spheres from the peak coordinates given in the documents examined in the MNI space (Talairach coordinates were converted to MNI if necessary using MNI in Talairachmapping; Lacadie*

et al., 2008). The peaks are classified by colour as follows: insula (yellow), ACC (red), frontal regions (dark blue), parietal regions (light blue), occipital regions (green) and subcorticella (violet).

I.7. Understanding the Potential Biological Mechanisms of Meditation

The most widely accepted explanation on how meditation might exert its biological impacts is that it acts via the relaxation response (Benson, Beary, & Carol, 1974a).

The relaxation response is a spectrum of psycho-physiological changes associated with reduced physiological arousal. Physiological arousal and the relaxation response occur as a result of activity converging on pathways within the autonomic nervous system. A brief explanation of the interactions between the autonomic nervous system (ANS), central nervous system (CNS) and the physiology of peripheral organs follows.

I.7.1. Physiological Arousal

The nervous system is comprised of the peripheral nervous system and the central nervous system. The peripheral nervous system is divided between somatic and autonomous nervous systems.The CNS is comprised of the brain and spinal cord (Brodal, 2010).

The ANS is further subdivided into the sympathetic nervous system (SNS) and the parasympathetic nervous system (PNS), both of which are fed by neuronal pathways stemming from the hypothalamus located in the CNS. Both the SNS and PNS regulate a range of biological functions over which we have minimal control. These include heart rate, breathing, digestion and regulation of blood flow (Brodal, 2010).

Physiological arousal occurs as a result of engagement with stimuli in the environment and has been a focus of psychophysiological research for several decades. Physiological arousal involves the activation of the SNS via hypothalamic projecting neurons from the CNS. The activation of the SNS stimulates the release of the catecholamines (epinephrine and norepinephrine) from the adrenal medulla. These catecholamines diffuse through the blood stream and act on receptors in various organs and also on blood vessels resulting in a number of effects which include: increased heart rate, increased heart contractility, increased blood pressure as a result of an increase in total peripheral resistance, increased sensory alertness, constriction of pupils, increase in electro dermal activity, increased

sweating and increased respiratory rate (Azarbarzin, Ostrowski, Hanly, &Younes, 2014; Bradley, Miccoli, Escrig, & Lang, 2008; Noteboom, Barnholt, &Enoka, 2001).

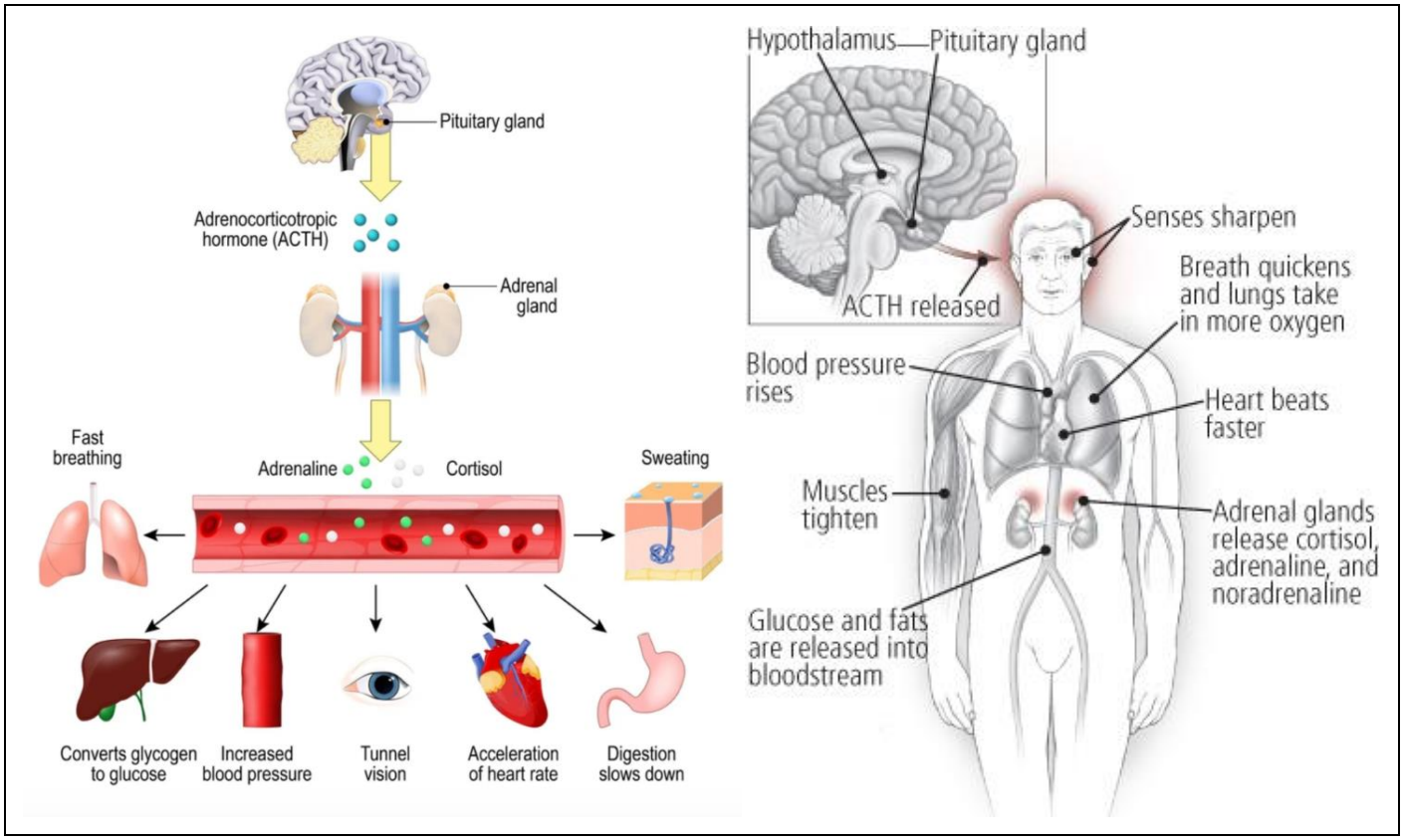

Figure 5: *The physiological arousal effect from the brain to organs.*

I.7.2. The Relaxation Response

The relaxation response is characterised by a decrease in SNS activity and an increase in PNS activity, essentially a reversal of physiological arousal, which leads to the following typical effects:

- Slowing of heart rate
- Decrease in respiration
- Decrease in metabolism
- Increase in salivation and digestion
- Decrease in blood pressure
- Increase in alpha activity in the brain
- Subjective feeling of relaxation
- Subjective feeling of warmth and heaviness.

The idea that meditation might work by eliciting the relaxation response has been investigated over the past few decades, with the first studies emerging in the literature in the 1970s. Since that time many studies were published that demonstrated that meditation was generally associated with physiological changes characteristically associated with a reduction in autonomic arousal. Herbert Benson pioneered this line of thinking with a series of studies that appear to demystify meditation by demonstrating that its main physiological effect was to reduce excitement. (Avorn& Benson, 1974; Benson, Beary, & Carol, 1974b; Benson, Dryer, & Hartley, 1978; Benson, Rosner, Marzetta, &Klemchuk, 1974; Benson, Steinert, Greenwood, Klemchuk, & Peterson, 1975). At first, these physiological changes were associated with Transcendental Meditation (TM), a highly commercialized form of meditation which in the 1970s and early 1980s achieved such popularity, at least in the West, was what people understood as meditation (Delmonte, 1984; Holmes, Solomon, Cappo, & Greenberg, 1983). However, Benson soon discovered that many different approaches to meditation also triggered the same process of de-arousal. These different approaches included simple relaxation methods and even practices not previously categorized as meditation such as certain forms of prayer. For example, a 1977 study comparing transcendental meditation, general relaxation training and muscle relaxation via electromyography biofeedback demonstrated that although the TM group significantly decreased physiological arousal, the other two control groups were equally as effective (Cauthen&Prymak, 1977). Another study comparing TM to listening to music found that both groups were equally effective in decreasing oxygen consumption and carbon dioxide production (Fenwick et al., 1977).

Benson coined the term “relaxation response” to describe this set of physiological responses (Benson, 1975). These findings represented a paradigm shift in the understanding of meditation and similar practices away from mystical and spiritual ideas and towards a more secular, non-denominational conceptualization. This led to the widespread assumption that meditation could be physiologically defined by the relaxation response. The idea has had traction ever since with many researchers and authorities (e.g. as stated earlier the US National Centre for Complementary and Alternative Medicine).

Although this way of understanding meditation was greeted with enthusiasm during the 1970s and 1980s, the fact was new studies provided evidence that many non-meditative strategies also elicited the relaxation response. Many researchers supported the notion that the definition of meditation should be allowed to expand and accommodate

strategies traditionally regarded as non-meditative but that could also elicit the relaxation response. Although this seemed like the easiest solution, it meant that almost any relaxing activity could be included in the definition of meditation.

Some researchers argued that rather than dilute the concept of meditation, a different definition of meditation was required to support the perception that meditation was a specific and distinct entity (Cardoso, de Souza, Camano, &Leite, 2004).

This dilemma underlines the necessity of a clear definition of meditation.Only then can we more fully test and hence understand the biological mechanisms by which meditation may act and how this differs from other non-meditative activities. The relatively nebulous and fluctuating conceptualisations of meditation appearing in both professional journals and popular media have served to exacerbate rather than resolve the intertwined questions about its potential mechanisms and how it might be defined.

I.8. Meditation and Stress Reduction

It is well established that meditation is able to reduce the negative dimensions of psychological stress (Goyal, Singh, Sibinga, & et al., 2014). The biological mechanisms by which it does so are still somewhat unclear. It is currently thought that meditation influences the body at a molecular level through the reduction in stress biomarkers and through the decreased expression of stress related genes.

A common biomarker associated with stress is the steroidal hormone cortisol. Researchers observed serum cortisol concentrations in meditators were significantly lower than compared to their control counter parts (Sudsuang, Chentanez, &Veluvan, 1991; Vandana, Vaidyanathan, Saraswathy, Sundaram, & Kumar, 2011). There was also widespread acceptance of other biomarkers for stress. Examples of these biomarkers include interleukin-6 (IL6), tumour necrosis factor a (TNF-a) and used C-reactive protein (CRP). Studies have shown that meditation also seems to influence the reduction of these markers of stress therefore giving us another possible mechanism through which it can exert its purported health effects (Creswell et al., 2012; T. W. W. Pace et al., 2010; Rosenkranz et al., 2013; Zgierska et al., 2008). It is also important to note that biomarkers and genes related to stress have a large degree of overlap with biomarkers and genes related to inflammation. Therefore, it may be possible that meditation’s biological effects are mediated through interplay between stress and inflammatory pathways.

I.9. Chronic Inflammation and Meditation

Meditation is a lifestyle modification that is commonly associated with reduction of stress. As mentioned previously, the connection between stress and the genesis of chronic inflammatory mediators is well documented (Steptoe Andrew, Mark Hamer, & Yoichi Chida, 2007). It is plausible therefore that meditation might have a positive influence on chronic inflammation by reducing stress and possibly other pathways (Chiesa &Serretti, 2009; Manocha et al., 2011). The impact of meditation on chronic inflammation, and hence the risk of developing non-communicable diseases (NCDs) (cardiovascular disease, cancer, respiratory disease and diabetes) can therefore be assessed by measuring its impact on chronic inflammation markers. Epigenetic studies offer a convenient and powerful method to assess the impact of meditation on NCD risk.

Inflammatory markers can be measured directly through serum concentrations and indirectly via gene chip array analysis. Gene expression levels can correlate, up to a certain extent, with concentrations of each inflammatory marker in the blood at the time the blood sample was taken (Vogel & Marcotte, 2012).

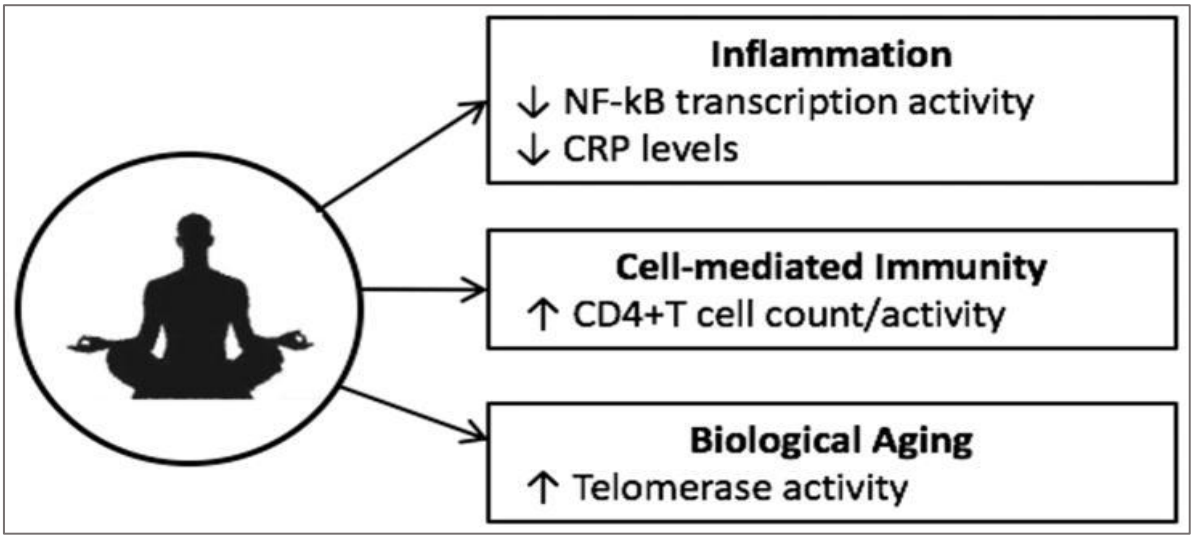

Figure6:*Meditation and immune system biomarkers.Studies revealed mediation is associated with changes in select immune system processes involved in inflammation, immunity, and biological aging. Nuclear factor-κB, NF-κB; C-reactive protein, CRP (David S. Black,George M. Slavich, 2016).*

In 2012, Antoni et al. reported that those who participated in cognitive based stress management therapy (CBSM), displayed significant down regulation of pro- inflammatory genes including IL6, TNF and IL1 (Antoni et al., 2012).

Three separate studies exploring other various techniques of meditation including hatha yoga, Kirtan Kriya meditation and relaxation response sequence have also displayed down regulation (i.e. a beneficial reduction) of pro-inflammatory genes (Bhasin et al., 2013; D. S. Black et al., 2013; Kiecolt-Glaser et al., 2010).

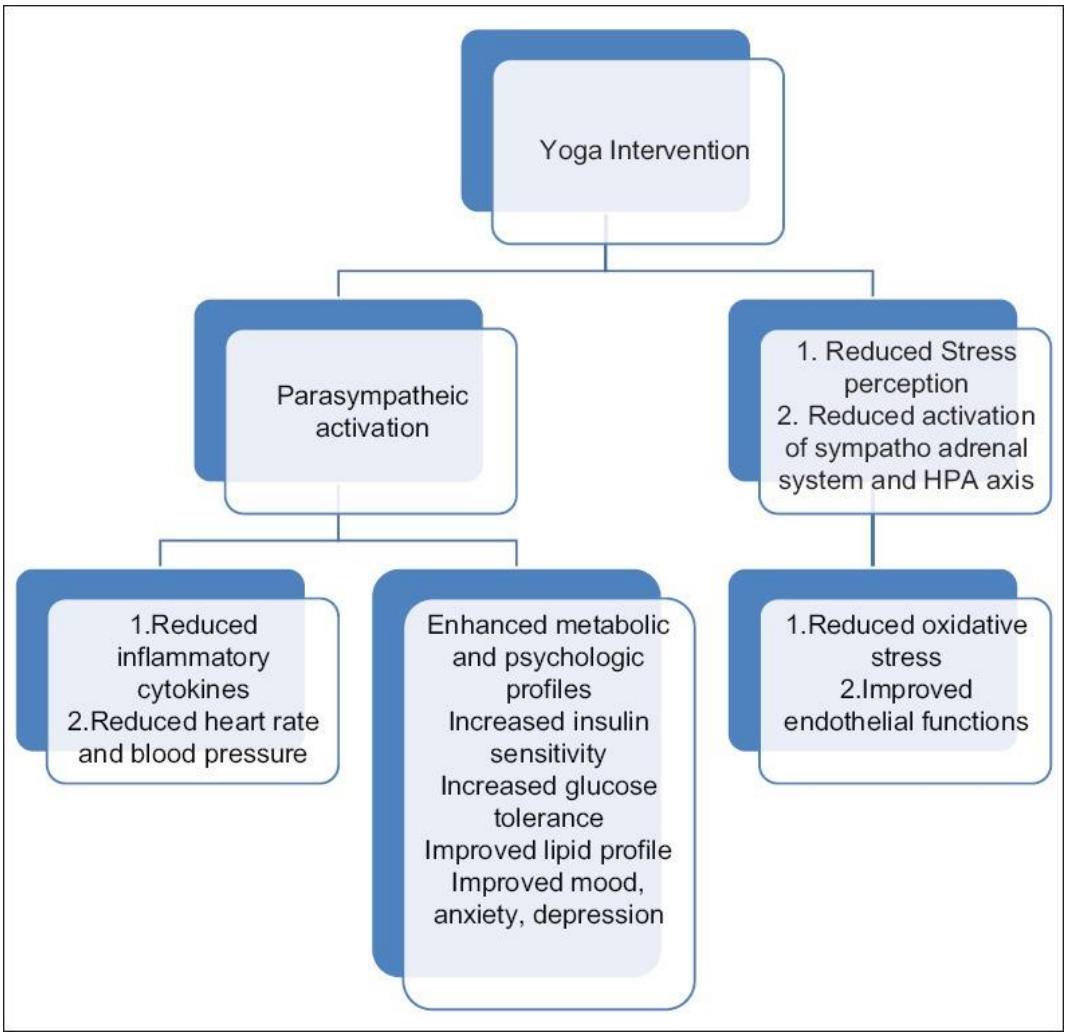

Figure7: *Yoga intervention pathways (Vijay Pratap Singh, Bidita Khandelwal, Namgyal T. Sherpa, 2015)*

I.10. Immune Function

The immune system is the collection of cells, tissues and molecules that mediate resistance to infections; its physiological function can be summarised as follows (Abbas & Lichtman, 2010):

- Defence against infections

- Defence against tumours
- Its ability to cause cell injury and also induce cell repair
- Clearance of dead cells
- Its ability to induce chronic or acute inflammation
- The recognition of tissue grafts and newly introduced proteins.

There are two main branches of the immune system the innate and the adaptive.

I.10.1. Immune Function and Meditation

There is emerging evidence that mind–body related practices such as meditation may be able to modulate the immune response either through increased levels of inflammatory markers (as discussed previously) or through the increased levels of immune cells (Infante et al., 2014; Morgan, Irwin, Chung, & Wang, 2014). In my literature review there's studies relating to immune gene expression changes (Antoni et al., 2012). This high-quality study found that cognitive based stress management increased gene expression for the following genes: type I interferon response (IFIT1, IFIT2, IFIT3, IFI44, IFI44L, ISG15, MX2, OAS2,OAS3), type II interferon signalling (IFNG) and interferon signal transduction (STAT1, STAT2). Interferons are involved in their anti- viral activity and therefore increased expression of these genes may lead to a superior anti-viral response than in those who did not meditate.

I.10.2. Cell Structure and Function

A relatively new idea is that meditation may influence the body through its actions on cell structure and function components. Cells are the underlying basis of all living life forms including humans. “Cell Theory” is one of the fundamental basic principles of biology and states (Schwann T, 1847):

- Every living organism has cells.
- The cell is the essential unit of life.
- Cells arise from pre-existing cells
- The flow of energy happens within the cells.
- DNA goes from cell to cell.
- Every cell has the same basic chemistry.Homeostasis is process by which cells maintain and regulate their internal environment in response to constant changes in

the external environment. The ability to maintain homeostasis is a function of how healthy a cell is and how long it can survive. A cell maintains homeostasis by controlling what enters and leaves it through its plasma membrane and thus controlling factors essential for survival. These include:

- Maintain intra-cell concentrations of metal ions in a narrow range.
- Removing waste products
- Regulating temperature
- Producing energy
- Maintaining a barrier from the external environment
- Producingcarrierproteinsandreceptorstorespondto theexternal environment
- Regulating gene expression.

The above list is by no means exhaustive and only highlights the basic processes that are required for cell homeostasis (John S. Torday, 2015). The genes that code for proteins involved in these processes are far larger in number, however they can broadly be categorised by the following:

- Heat shock proteins
- Enzymes
- Membrane transporters
- Ion channels
- Ligand gated ion channels
- G-protein coupled receptors
- Cell structural proteins.

Numerous studies and reviews have already established that psychological stress can shorten the lengths of structures called telomeres (Figure 8) (Epel et al., 2004; Oliveira et al., 2016; Starkweather et al., 2014; Tzanetakou, Nzietchueng, Perrea, &Benetos, 2014). Telomeres are DNA sequences at the end of each chromosome that protect it from nucleolytic degradation, unnecessary recombination, repair and inter- chromosomal fusion. Every time a cell divides, the telomere shortens and as this continues, it eventually induces cell senescence (which leads to cell death).

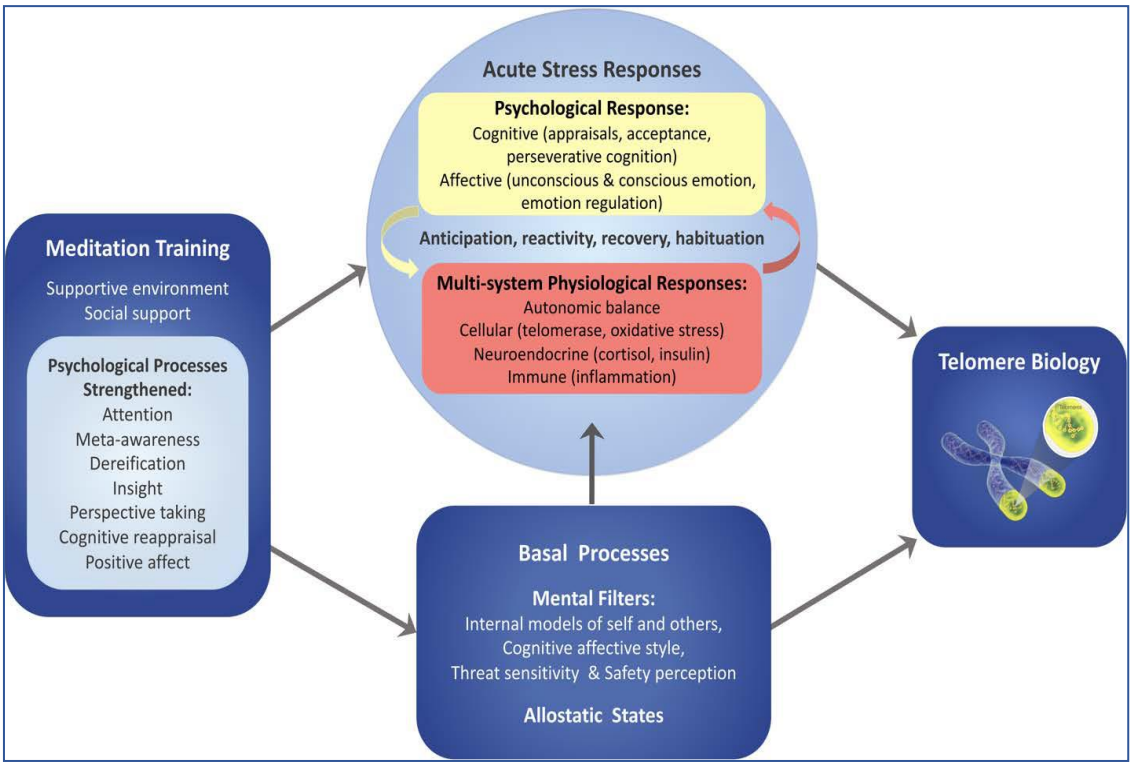

Figure 8: *A theoretical model depicting how meditation training impacts telomere biology via stress processes (Epel ES et al, 2018). Meditation training alter basal processes that influence acute stress responses, potentially resulting in fewer overall stress reactions. Training can also provide tools to reduce the severity of acute reactions when they take place.(Quinn A Conklin et al, 2018).*

As discussed previously, meditative practices have been shown to reduce stress and stress biomarkers. The connection between stress and telomerase led researchers to investigate the link between mind body practices, such as meditation and whether or not they are able to influence telomerase activity. The literature surrounding this notion has grown over the past 5 years and a number of publications confirmed the idea that meditative practices might beneficially influence the activity of telomerase and thus prolong cell life (Jacobs et al., 2011; Kumar et al, 2015; Lengacher et al., 2014).

Additionally, a 2013 meta-analysis of four mindfulness meditation RCTs concluded that mindfulness significantly increases telomerase activity in peripheral blood mononuclear cells (Schutte&Malouff, 2014).

Based on these studies it may be plausible to expect that mental silence may alter telomerase or the expression of its related genes and give us another possible explanation of how it might exert its biological effects. In addition, it is also possible that the two

different definitions of meditation may alter the expression of other cellular structure and function genes. However, since these genes are involved in an exponential number of gene pathways, it would be impossible to determine the impact on the human body.

I.11. Study Aims

The aim of this study was to determine firstly, whether meditation and MBI's has any specific effects on the practitioner, and secondly whether there are differences between different types of meditation. It was expected that different types of meditation are capable of invoking specific effects in the practitioner. These specific effects are thought to manifest as gene expression changes, which would be measured through specific analysis.

CHAPTER TWO
METHODS

II.1. Criteria for Considering Studies

In this study we will see the materials and methods used by reaserchers on the topic of understanding mind body interventions (mindfulness, yoga, RR, Tai Chi, and Qigong …etc) that include gene expression analysis, in order to assess the evidence for their effects on gene expression, and what changes in gene expression underline the mental benefits of MBIs. The studies were identified using the following keywords combination: (mindfulness, meditation, relaxation response, tai chi, yoga, qigong) and (expression of genes or microarrays or transcriptomes). We've previewed at first to study articles that studied the impact of physical activity, diet, MBI's and electromagnetic fields effect (that were 8 articles) on gene expression and modulation against stress, but all those topics has been excluded and we've only focused on MBI's. More-over there's 10 articles which has been studied, including 2 reviews and 8 reaserch articles. The studies that met the following eligibility criteria were included:

1.The study population must be consistonly of adults.

2.Clinical and non-clinical samples were authorized (for example, students, cancer patients and caregivers) and studies of all sizes were included.

3.Studies with experienced or inexperienced practitioners were allowed.

4.Changes in gene expression had to be one of the outcome variables (any number of genes analyzed, any cell type (PBMC had all the focus) and any gene expression technology were allowable).

5. The independent variables had to be any type of MBI's.

6. Research and review articles were included; comments and conference proceedings were excluded.

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  As an outcome there was 0% plagiarism and 100% uniqueness.

II.2. Analysis Procedure:

We've described the analysis procedure briefly in a general way, which applies on all the articles studied and as shown in Table 1.

First, people has been selected and categorized from a larger pool of volunteers into two demographically well-matched groups of control and practitioner groups, for comparison. They have been submitted to different types of mind body interventions and then the following brief procedures were made:

- Blood samples were collected from each participant before and after the intervention period.
- Preparation.
- Extraction, Concentration Measurement, and Integrity Check.
- Whole-GenomemRNA Expression Using different technologies as shown in the Tables below.
- qPCRAnalysis.

Table 1. *summary of materials and methods used in every study.*

Study	Participants	Type of population	Intervention	Sample/ cell type
KN Harkess et al. (2016)	N= 26	Stressed women	Yoga 1hour/week During 8weeks	Blood
Bhasin et al. (2018)	N= 24	Hypertensive	Relaxation response (RR) 20min/week During 8 weeks	PBMCs
Lengacher et al. (2014)	N= 28	Breast cancer patients	Variation in MBSR 6 weeks	PBMCs
Chaix et al. (2017)	N= 18	Long term meditator	Mindfulness and sitting mediation 30min/day 3 years	PBMCs
Jacobs et al. (2011)	N= 30	Retreat participants	Meditation 6h/day 3 months	PBMCs
Conklin et al. (2018)	N= 28	Retreat participants	Silent meditation (sitting and moving) 30-45min for a total of 10h a day 3 weeks	PBMCs
Wenuganen et al. (2021)	N= 23	Healthy practitioners	Transcendental meditation (TM) Twice daily 40 months	PBMCs
Louks et al. (2016)	N= 399	New EnglandFamily (NEFS)	Mindfulness	PBMCs
Yang et al. (2021)	N= 22 - 1895	Patients with Type 1 and Type 2 Diabetes	Sitting and moving Meditation Mindfulness, yoga, qigong, tai chi, CBT, MBSR, RR 10-240 min/day 5 - 52 weeks	PBMCs
Buric et al. (2017)	N= 6- 40	Normal population = 50% Stressed populations =50% (33% breast cancer + 22% caregivers + 45% others)	Mindfulness = 22% RR= 17% DifferentMBI's= 61% Moving interventions = 44% 46% of interventions duration 8–12 weeks; 33% of interventions had only weekly meetings	72% of from PBMC, 17% from lymphocytes the left percentage is divided between peripheral blood neutrophils and whole blood.

CHAPTER THREE: RESULTS AND DISCUSSION

Below we present the brief results of each study relying mind body interventions and their outcome:

Table 2. *Summarized obtained results in every study.*

Abbreviations: Il= Interleukin, Bp=blood pressure, Tnf= Tumor Necrosis Factor, Tl =Telomere Length, NF-κB= Nuclear Factor Kappa B, NFATC2 =Nuclear Factor Of Activated T Cells 2, Ta= Telomer Activity, CD2=cluster of differentiation 2, IEAA= Intrinsic Epigenetic Age Acceleration, ↑ increased, ↓ reduced

Study	Outcome
KN Harkess et al. (2016)	↓ DNA methylationTNF at CpG 4/5/6 Non significant↓ IL6
Bhasin et al. (2018)	↓ Blood Pressure (BP) in ≥ 50% of patients 1771 genes regulated 84 genes ↓ immune system molecules (CD2, TLR4,TLR7,TLR8,TLR9,NFATC2,NF-kB,IL-15,IL-18,IL-2,IL-3,TNF) 88 genes ↑ cell growth, immune system molecules, glucose metabolism, cardiovascular system, circadian rhythm.
Lengacher et al. (2014)	↑ Telomere Activity(TA) Ns Telomere Length (TL)
Chaix et al. (2017)	↑ IEAA
Jacobs et al. (2011)	↑ TA
Conklin et al. (2018)	↑ TL Ns TA
Wenuganen et al. (2021)	See table 3 and 4
Buric et al. (2017)	81% of studies got a reduction in inflammation related genes and/or transcription factors
Louks et al. (2016)	20% ↓ risk of Type 2 Diabete
Yang et al. (2021)	Most studies revealed a reduction of blood glucose and inflammation related genes and aging mechanisms.

Hence, down below we present further the results and discussion of every study:

III.1. Yoga intervention for stressed women, lowers DNA methylation in whole TNF and specific sites, but no evidence for inflammatory protein markers reduction (KN Harkess and collegues, 2016)

Results:

They obtained in their results the following analysis of inflammatory markers (KN Harkess et al., 2016) :

Analysis of DNA methylation: No differences in mean methylation between groups in CRP or IL6 regions were observed in the analysis of the covariance model. A major significant group effect was found for mean TNF methylation, accounting for 19% of the variance.There seemed to be group differences at the different TNF sites, but this varied with the inclusion of covariates, No evidence of differences in methylation at individual units of CpG LINE-1, nor the total mean, was demonstrated. Covariates were also not associated with differences in LINE-1 methylation (Cohen J, 1988).

Regions of methylation :The yoga intervention was associated with a reduction in TNF methylation and decreased IL6, although this did not reach significance. Individual CpG units. Significant associations indicating a decrease in post-yoga time point methylation have been demonstrated for TNF sites CpG 1 and 4/5/6.

Exploring Mental Health Measures : Perceived stress is strongly correlated with psychological distress. Subjective well-being, perceived stress, and emotional distress are moderately correlated.

Discussion:

In the study of KN Harkess et al (2016), the prospective pilot trial explored the relationship between yoga, psycho-physiological indicators of health, and markers of inflammatory protein and methylation in a stressed female community population (KN Harkess et al., 2016).

The yoga group showed lower DNA methylation in the TNF area as a whole, and at specific sites, in the cross-sectional analysis compared to the control group. It should be noted that we found no evidence of a combination of yoga and serum measures of inflammation. This could potentially account for our reported hypomethylation of TNF in

our yoga group and following yoga intervention (Vogelzangs N et al, 2013 ; Leonard B et al, 2012 ; Loftis JM et al, 2008)

There is some limitations in this study, first is that it was a pilot study with only limited statistical power. As a result, this limited statistical analyses that could be undertaken, in addition to having low power when measuring the group differences DNA methylation measurement, which means that we can't draw causal conclusions about differences between groups. The methylation of the DNA studied was derived from DNA extracted from peripheral total blood, which is consistent with our concurrent exploration of serum markers of inflammation.

The lack of association between DNA methylation markers and serum markers of inflammation makes interpretation of functional impact difficult, although this may be due to statistical power and the possibility that methylation may less immediately affect serum protein expression levels.

As stress has became the problem of the century (Cassey L, 2014) a higher disease stress related is more probable to occur (McEwen BS, 2006; Cohen S, 2007; Segerstrom SC, 2004) As a result, future prospective studies should continue to explore the relationship between stress and inflammatory biomarkers in community populations. It is recommended to replicate this study in a much larger sample and including analysis of DNA methylation profiles at baseline (KN Harkess et al, 2016).

III.2. Lowered blood pressure in half of hypertensive patients responders to the RR intervention, followed by a strong association with immune and inflammatory regulation (Bhasin and collegues, 2018)

Results:

Gene expression were identified differentially in the BP responders and the non respoders In both BP responders, they identifed in the analysis 1821 and 1280 differentially for 10 non responders and 12 responders, later Venn diagram analysis identified 50 transcripts changed after RR intervention, that was shared between both groups as it is shown in Figure 9. However, 1771 transcripts were uniquely altered after RR intervention in the BP responders (Bhasin et al., 2018).

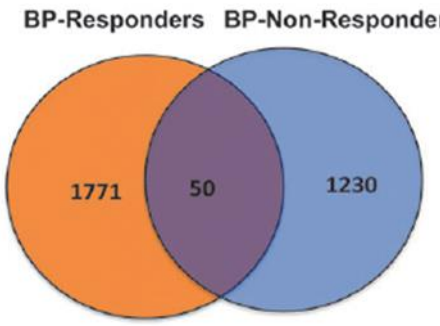

Figure9:*Transcriptome changes distinguishing BP responders from nonresponders after 8 weeks of RR intervention.*

Venn diagram depicting common genes between BP responders and nonresponders and transcripts selectively changing in responders or nonresponders only. Fifty genes were commonly altered between BP responders and nonresponders. (adapted from figure 4 of the article of Bhasin et al., 2018)

The analysis of the 84 downregulated genes of the RR HTN Responder Signature predicted inhibition of multiple molecules of the immune system [e.g., CD2, several members of the toll-like receptor (TLR) family. (TLR4, TLR7, TLR8, TLR9), NFATC2, nuclear factor-kB (NF-jB) (complex), IFNG, CD40LG, tumor necrosis factor (TNF), interleukin (IL)-15, IL-18, IL-2, IL-3].

After a leading edge analysis there's been genes that are believed to manipulate the phenotype, and are the important genes for formulating a hypothesis about the genetic mechanism underlying the potential impact of RR on BP.

This analysis identified many nuclear transport, cell cycle, protein kinase cascade, and insulin receptor signaling pathway-related genes (NUP43, NUP50, NUPL1, NUP188, RANBP2, TPR, POM121, NUP153, CTNNB1, PIP5K1C, PIK3R1, MAPK8, PIK3CB, PIK3CD, and JUN) as most relevant genes that may be critically implicated in BP response after an RR intervention in HTN patients.

The regulator network indicates that the RR may affect inflammation by regulating the anti inflammatory pathways [i.e. ,signalinggluco corticoid (GC) receptors] and by regulating the NF-kB and TNF pathways. Interactive networkedanalysis of RR-affected genes among identified NF-kB respondents and associated downstream targets as critical concentration centres.

Most genes upregulated and downregulated of NF-kB decreased among respondents, giving the first indication that NF-kB could play a critical role in mediating the effects of RR on HTN.

NF-kB could play an important role in realizing the benefits of RR. NF-kB has also been identified as a key molecule of interest in previous studies (KuoB,et al,2015) to identify genomic determinants of RR in healthy subjects. As and also in the study of the effects of RR on patients with irritable bowel syndrome and inflammatory bowel disease (KuoB,et al,2015).

Discussion:

According to Bhasin et al (2018), the RR intervention for non-medicated patients with stage 1 HTN demonstrates that BP is effectively lowered in over half of all patients following 8 weeks of RR formation and is associated with improvements in psychological variables and specific changes in gene expression. Even thought his evidence is compelling and suggests a direct effect of relaxation response on blood pressure (Bhasin et al., 2018).

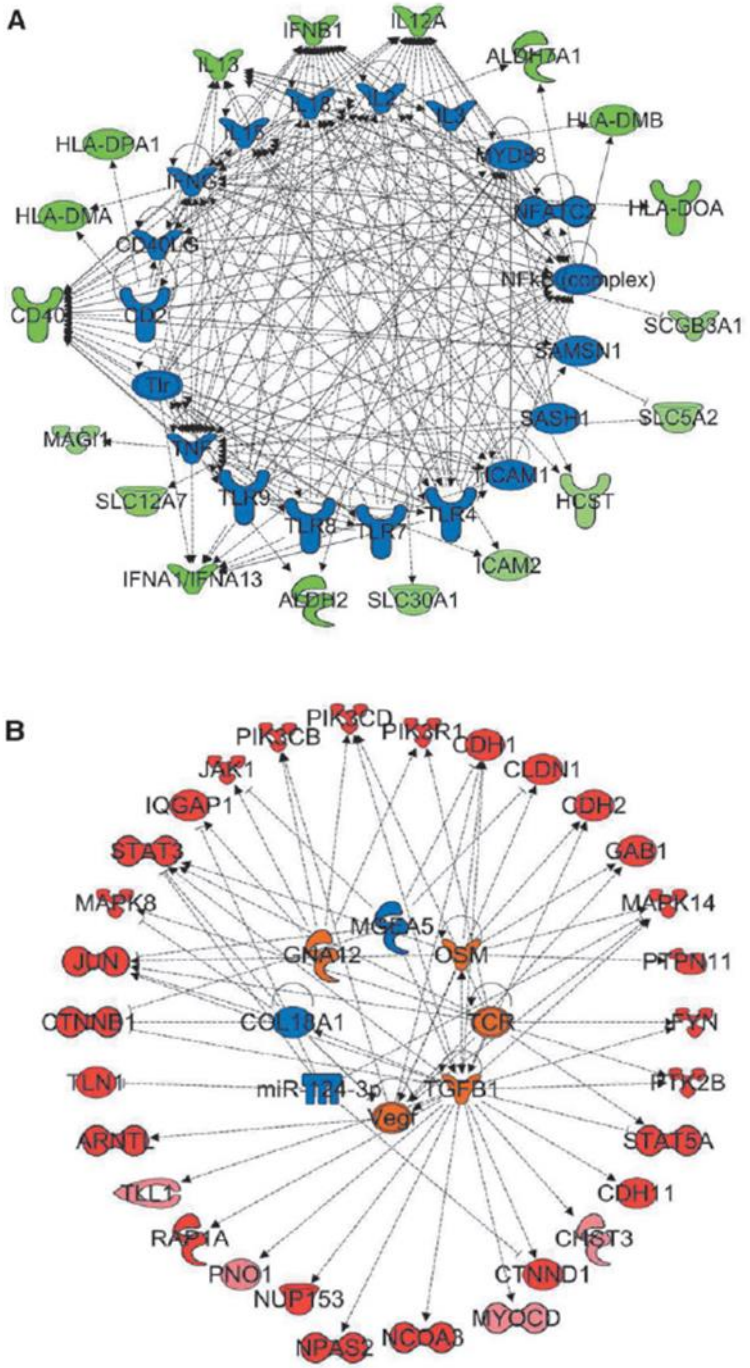

Figure10:*Upstream regulatory assay of genes significantly related to BP response in HTN patients.Upstream regulator analysis of genes significantly linked to BP response in HTN patients. This analysis assists in identifying upstream regulators that should be significantly activated or inhibited prior to alterations in gene expression after RR formation.Keyupstream regulators identified from the analysis of down-regulated (A) and up-regulated (B) genes of the HTN Responder RR signature. Upstream regulators which should be switched on and off are orange and blue respectively. Targets downstream from each controller are indicated in red (genes upregulated by RR) and green (genes*

downregulated by RR). BP, blood pressure; HTN, hypertension; RR, relaxation response (adapted from figure 7 of the article of Bhasin et al 2018).

The BP improvements observed in this study are consistent with the changes observed with medication of anti-hypertensive(Musini VM et al.,2012 ; Bangalore S et al., 2007) and align with related work demonstrating the impact of MBIs on BP in various populations. (Dusek JA et al., 2008 ;PaltaP et al.,2012 ; Schein MH et al.,2009), this is the first study to test such a procedure for a population of untreated adults with carefully documented persistent HTN and the first study to identify the genomicdeterminants of MBI's impact on HTN.

The determinants associated with a MBI's impact on HTN and The results of this study provide new perspectives on how integrative medicine, particularly mind-body approaches, could influence the BP control at a molecular level.

The most consistent pathways that emerged from these tests were inflammation / immune response, including targets downregulation of NF-kB, selectively influenced among BP respondents following the RR practice. There is considerable evidence from data analysis to support the apparent key function of NF-kB in mediation. At least some of the beneficial effect of RR on BP reduction. Firstly, the advanced identified analysis, among the most systematically responding-specific upregulated genes, mainly those involved in nuclear transport (NUP43, NUP50, NUPL1, NUP188, RANBP2, TPR, POM121, and NUP153)

Modified nuclear transportation plays a key role in the effects and impacts of oxidative stress on nuclear transportation and the redistribution of NF-kB, a key regulatory mechanism in the activation of NF-kB.

Earlier work by the authors suggests that actually, different interventions can be done through different mechanismsImportantly, this integrated RR HTN Responder signature of 172 genes reinforces the involvement of NF-kB in mediating RR-related improvements in BP, as demonstrated by the most significant fortification of pathways of transmission between down-regulated genes associated with immune function and inflammation (for example., NF-kB signalling,crosstalk between dendritic cells and NK cells,T-cell differentiation, IL-12 signalling and generation of macrophages, TREM1 signalling,communication of cytokines between immune cells, pathways of presentation of antigens, signalling of TLR and communication between innate and adaptive immune cells).

They also observed an association between reduced innate immune activity (TLR signalling) and reduced BP after the RR intervention is further strengthened by upstream regulator analysis, which predicts a reduction TLR activity (TLR4, TLR7, TLR8 and TLR9) based on reduced expression of multiple downstream target genes (ICAM2, SLC30A1, ALDH2, IFNA1, IFNA13, SLC12A7 and CD40). TLR activation in vascular or renal lesions associated with HTN has been described in re-eclampsia, renal disease, spontaneously hypertensive rats, and angiotensin II-induced HTN.. The fact that TLRs can play an important role in HTN is supported by the conclusion that inhibition of TLR with neutralizing antibodies has resulted in a reduction of BP and a down-regulation in NF-kB, ICAM1, chemokine and cytokine regulation (McCarthy CG et al., 2014 ; Singh MV et al., 2014).

Both health education and RR appear to reduce BP in a large proportion of patients. However, only RR also reduces the medications of BP requirements, suggesting mechanistic differences between RR and health education interventions (DusekJA,et al,2008).

III.3. Changes in TL and TA in breast cancer patients after MBSR intervention (Lengacher and colleagues, 2014)

Results:

They've found in their study that the participants charachterestics that 72% were non-Hispanic White 78% had Stage I or II cancer and 36% received both chemotherapy and radiation (Lengacher et al., 2014).

The change observed in the TL and TA practicing MBSR (BC)

TL values were the same at baseline, 6-week follow-up, and 12-week follow-up between the MBSR(BC) and usual care (UC) groups (Figure 11, $p > .05$ for all comparisons). Therefore, there was no indication that participation in the MBSR(BC) program had a differential effect on the change in TL. On the other hand, the TA increased steadily over time in the MBSR(BC) group, but remaind relatively constant at the reference level in the UC group (Figure 12).

At baseline participants who were randomly assigned to MBSR (B.C.) had lower reference TA values (intercept) than those assigned to CU ($p = 0.04$). Taking into account this reference difference, the mixed linear model confirmed a steeper slope (greater improvement) of the 12-week TA in the MBSR(BC) group relative to the UC group.

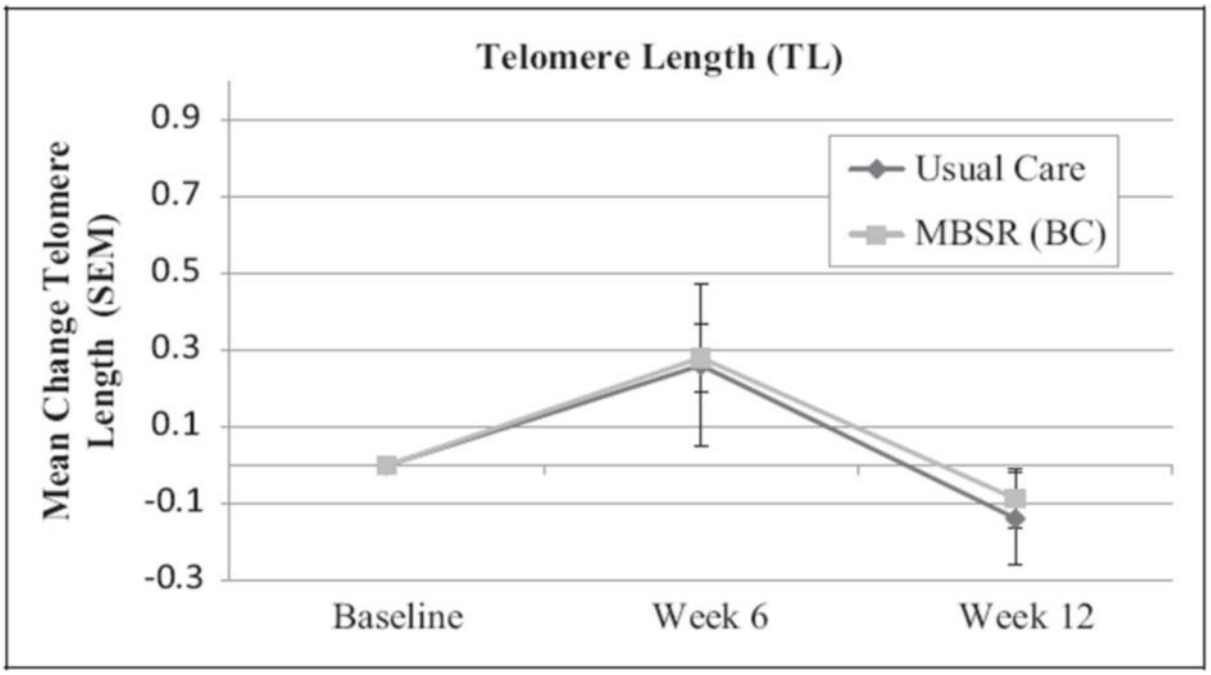

Figure11:*Mean change from baseline log length of telomeres (with mean standard error) in randomized breast cancer survivors for mindfulness-based stress reduction (MBSR(BC)) or the UC group.*

Baseline measurements were adopted before the intervention began. at the end of the intervention on week 6 measures were taken and after the end of the intervention after 12 weeks,another measures were taken (Lengacher et al., 2014).

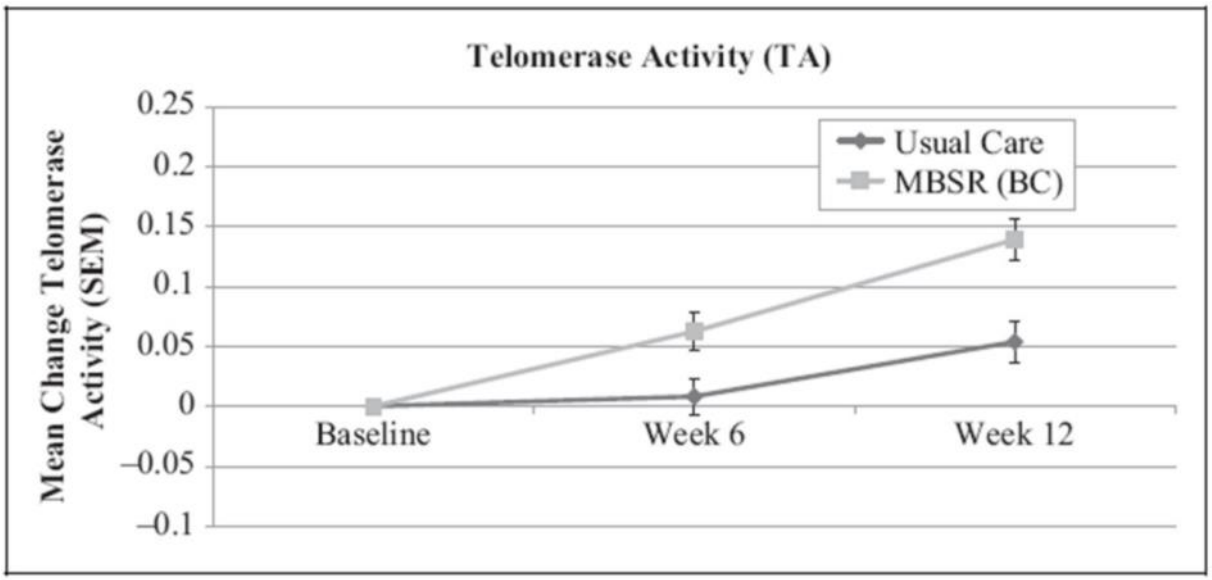

Figure12:*A mean change from baseline in log-transformed telomerase activity among BC survivors randomized to the mindfulness-based stress reduction for breast cancer [MBSR(BC)] or UC groups.*

A linear mixed model indicated a higher slope (increase) in TA for the MBSR(BC) group compared to UC ($p < .01$). Before the start of the intervention at baseline measures were taken, at the end of the intervention on week 6 measures, and week 12 follow-up measures 6 weeks after finishing the intervention (Lengacher et al., 2014).

Discussion:

According to Lengacher and collegues(2014) The reasearchers that did this present study assume that this is the first randomized controlled trial that has examined the effects of MBSR(BC) on TL and TA in PBMCs from BC survivors (Lengacher et al., 2014). They got as a result after the MBSR(BC) intervention a considerable increase of TA among BC survivors over time from baseline to 12 weeks. These data suggests an ongoing post-treatment effect of the MBSR(BC) program on TA, at least in the short term (end of MBSR(BC) to week 6 to week 12). However, their research found a higher psychological status being associated with higher TA. Contrary to the TL were they haven't found any evidence that links the MBSR(BC) program with a change in it (Lengacher et al., 2014).

This study shows that there's a strong link between a stress-reduction intervention and increased TA.

As depicted in Figure 12, TA increased approximately 17% over time in the MBSR(BC) group compared to approximately 3% in the UC group. TA has the capacity to add DNA sequences, thereby actively increasing TL and preserving healthy cell function (Kim et al., 2003). TA has the ability to add DNA sequences, thus actively increasing TL and maintaining healthy cellular function (Kim et al., 2003). While there has not been a significant increase in the TL in the MBSR(BC) group, where the cause may be due to the lack of intervention duration as Ornish et al. (2008) suggest that the changes in TL linked to cognitive interventions may take at least a full year to show the influence. Therefore, TA may be more sensitive to subtle changes over relatively short times as compared to TL and until now, it is considered that the increased TA associated with the MBSR(BC) program shows a great impact on cellular aging decrease. Furthermore, Lin and colleagues (2010) reported significant variations in TA between cell types, with B cells having a higher TA than T cells.

Prior research has shown, in fact, that patients receiving MBSR have increased mindfulness which leads to diminishing the stress perception and improved quality of life in nonclinical populations (Nyklicek&Kuijpers, 2008 ; Shapiro, Oman, Thoresen, Plante, & Flinders, 2008), decreased perception of stress and post-traumatic avoidance symptoms and improved positive mental states in cancer patients who are not receiving treatment (Branstrom, Kvillemo, Brandberg, & Moskowitz, 2010).Reduced anxiety and worry in patients suffering from anxiety disorders (Vollestad, Sivertsen, & Nielsen, 2011). Improved perception of control and fewer neuroticisms overall (two major stressors), both of which have been linked to TA (Jacobs et al., 2011). Furthermore mechanisms were meditation may improve cellular longevity including the reduction of stress hormones levels and oxidative stress and secreting higher levels of hormones that are beneficial to telomeres (Epel et al., 2009) and to the TA (Daubenmier et al., 2011). Study found that low TA is associated with an over autonomic responsiveness to acute mental stress and high levels of epinephrine at night whereas shorter LT is associated with higher levels of catecholamine and cortisol (Epel et al., 2006). Therefore, the level of TA to be somewhat sensitive at a cellular level to changes in psychological well-being (Epel, 2012).

III.4. The protective role of years of mindfuleness and sitting meditation practice from accelerated epigenitic aging in older adults, with an increase of calculated Intrinsic Epigenetic Age Acceleration (Chaix and colleagues, 2017)

Results:

They obtained in their results a DNAm and chronological ages were highly correlated to each other, confirming the accuracy of the epigenetic clock model. They calculated the Intrinsic Epigenetic Age Acceleration which adjusts the epigenetic aging rate for blood cell count estimates, leading to a measure unaffected by both variation in chronological age and blood cell compositionand found a significant negative correlation between meditation years of practice and IEAA in subjects aged 52 while such an effect was not found in younger subjects. (Chaix et al., 2017).

Discussion:

In the study of Chaix et al (2017) it is consisted of knowing If the epigenetic aging rate is long-term A meditator is not the same as a meditative controller. Chaix et al found no difference between them. However, they found that the IEAA course of the control and meditators varied with age, and the IEAA increased with the age of the control One of the described factors that accelerate epigenetic aging (Zannas et al., 2015). This research Shows that meditators' psychological stress is relieved by regular practice May contribute to IEAA stability across age groups compared to controls Controls were included in this analysis as « zero meditation experiences », significant effect Years of meditation on IEAA were only found in subjects ≥ 52 years old, suggesting that this is indeed the case. The protective effect of meditation practice was mainly observed in older subjects. Taken together, these results suggest a protective effect of meditation on epigenetic accelerated aging, Can be incremental and cumulative.

Data given here extend previous proof showing the influence of meditation coaching on aging biomarkers, notably the presence of longer telomeres in semi permanent meditators (Alda et al., 2016) a Hinduism meditation coaching (Lavretsky et al., 2013) and a mindfulness-based stress reduction program (Lengacher et al., 2014). End length and epigenetic aging rate, however, are shown to be reciprocally unrelated and severally joined to disease and mortality risk, in all probability through totally different aging signal pathways (Marioniet al., 2016). Previous reports on end biology, at the side of our

findings on epigenetic aging, counsel that meditation observation could modulate totally different molecular mechanisms involved in cell aging and will represent a helpful preventive strategy for age-related chronic diseases.

Our information could contribute to reveal the advantages of long meditation on healthy aging although they give many limitations that warrant additional investigation. It's conjointly crucial to explore in future studies the kind of practices and therefore the frequency and length of the training that might expeditiously decrease the epigenetic aging rate in otherwise meditation-naïve healthy subjects or clinical populations.

III.5. Increased telomere activity associated with psychological outcome after a meditation practice in retreat participants (Jacob and colleagues, 2011)

Results:

They have found that the telomerase activity was significantly greater in retreat participants than in controls at the end of the retreat ($p< 0.05$). Increases in perceived control, decreases in neuroticism, and increases in mindfulness and purpose in life were more pronounced in the retirement group ($p< 0.01$). Mediation analyses indicated that the effect of retirement on telomerase was mediated through increased perceived control and reduced neuroticism. In return, changes in perceived control and neuroticism have both been partly mediated by increased mindfulness and purpose in life. Moreover, the increase in purpose in life was directly responsible for the difference among telomere groups, while the increase in mindfulness was not (Jacob et al., 2011).

Discussion:

In Jacob & Al (2011) study, they claim that it is the first study that establishes a link between meditation and positive psychological change and telomerase activity. While they did not measure the baseline activity of telomerase, the data suggest that increases in perceived control and decreases in negative affectivity contributed to an increase in telomerase activity,This has consequences for the length of telomeres and the longevity of immune cells. In addition, the purpose in life is influenced by meditation practice and directly affects perceived control and negative emotion, directly and indirectly affecting telomerase activity.

III.6. The effect of silent meditation in retreat participants on TL, TA and psychological alterations (Conklin and colleagues, 2018)

Results:

Telomere length : There was no effect of group, but there was a significant effect of time and a significant interac-tion between group and time, such that retreat participants showed an estimated increase of 0.046 units in t/s ratios across assessments, com-pared to controls. There was no change in controls, and no considerable difference between groups at either assessment (Gardner et al., 2014 ; Robles-Espinoza et al., 2015).

Telomerase activity : Contrary to our hypotheses, there was no significant effect of time or interaction between group and time on TA. Neither age nor gender significantly predicted TA when covariates were included in the model.

Relations between telomerase activity, telomere length, and retreat experience: Changes in TA were also uncorrelated with changes in TL across assessments. To further characterize this relationship, we entered TA, time, and the interaction between TA and time into a model predicting TL in retreat participants only, with age and gender included as covariates. This model revealed a significant interaction between TA and time at post-assessment was also negatively correlated with retreat participants estimates of the number of hours they had spent meditating during retreat (Lin et al., 2016, 2010).

Telomere-related genes: The retreat group exhibited significant changes in 17 genes that did not differ between groups at pre-assessment. Significant group differences were observed at post-assessment for eight of these genes. Of these, only Cct2 exhibited a significant group difference during the pre-assessment. There were no significant changes in the remaining 28 genes for either group.

Discussion:

According to Conklin et al (2018), the apparent telomere increase observed in the retreat group was equivalent in magni-tude to the decline typically observed over about 4 years of aging. (Müezzinler et al., 2014). Interestingly, we found that retreat partic-ipants' TA levels at post-assessment were inversely related to mea-sures of retreat engagement, and to indices of prior meditation experience Many studies indicating an increase in TA have used statistical tests at a tail, with the assumption that TA will increase with the practice of meditation.. It is also notable that several studies have reported significant findings in

active control groups, suggesting TA may not be sensitive to meditation specifically, but to health-enhancing interventions more generally (Lin et al., 2016, 2010) .Retreat participants also showed higher expression levels of CTC1, UPF3A, UPF1, ATRX, ATM, and ATR, which are involved in telomere replication, repair, and maintenance. CTC1 is a compo-nent of the CST complex, which functions in telomere replication. UPF1 interacts both with telomerase and the telomeric fac-tor TPP1. UPF1 sustains telomere leading-strand replication, and its depletion leads to telomere instability owing largely to inefficient telomere leading-strand replication Lei et al., 2004, 2003 ; Nandakumar et al., 2012), .

Neuroticism concerns how easily or often a person becomes upset or distressed, and is closely related to constructs of anxiety and depression. While TL was significantly linked to anxiety and depression overall, neither baseline anxiety nor retirement anxiety decreases predicted changes in TL.. Despite the concep-tual relatedness of neuroticism, anxiety, and depression, our results point to heterogeneity in their consequences for telomeric regulation (Meier and Robinson,2004).

Thus there's some limitation and suggestions accordding to conklin et al (2018) PBMCs, which consist of many different cell types, including mono-cytes and lymphocytes. Lymphocyte redistribution, which can occur temporarily in response to acute stress may lead to 'pseudo-lengthening,« whereby average TL measurements increase due to an increase in cell types having longer telomeres (Dhabhar, 2011 ;Dhabhar et al., 2012 ; Rosenberger et al., 2009) It is possible that meditation training reduced the stress responsiveness of retiring participants, thus minimizing stress-related cellular redistribution during blood collection after assessment. There are many ways that changes in cell types could produce a pattern of telomere elongation, and because we did not measure per-cell telomere length changes, we label the phenomenon here ''apparent telomere lengthening,» and await fur-ther evidence of true per cell telomere lengthening in humans.

III.7. Transcriptomics and long term Transcedental Meditation (Wenuganen and colleages, 2021)

Results:

It is demonstrated as an obtained results in table 3 and table 4.

- Gene Ontological Process Terms: In the ontological process there's 200 different genes expressed associated with 12 terms to known effects of the TM practice program (Table 3).

Table 3.*Gene Ontological Process Terms*

Term	**Genes Downregulated in the TM Group**
Blood Coagulation	*F2RL3, CAV1, ITGB3, MMRN1, GP9, VWF, GP5, GP6, THBS1, TREML1, PROS1, ALOX12, ITGA2B, HBD*
Cell Activation	*F2RL3, CAV1, BCR, SNCA, TNFRSF13C, PAWR, ITGB3, GP9, VWF, GP5, GP6, THBS1, TREML1, WNT7A, ALOX12, ITGA2B*
Response to Stress	*SLC8A3, F2RL3, CAV1, CDC14B, SNCA, SLC6A4, FSTL1, PAWR, ITGB3, MMRN1, TRIM10, GP9, GP5, ALAS2, GP6, DDX11, PLOD2,CFH, MGLL, THBS1, HBD, BCR, PTPRF, SOCS3, LMNA, HBA2, HBA1, PTPRN, VWF, SH2D3C, TGFB1I1, TREML1, PROS1, ITGA2B, ALOX12*
Exocytosis	*VWF, ANK1, BCR, SNCA, SYTL4, ITGB3, THBS1, MMRN1, PROS1, ITGA2B*
CellAdhesion	*CAV1, PTPRF, CALD1, TNFRSF13C, ITGB5, ITGB3, PAWR, MMRN1, GP9, KIFC3, VWF, GP5, CD22, CNTNAP2, SGCE, TGFB1I1, LAMC1, THBS1, JAM3, ALOX12, ITGA2B*
Hematopoiesis	*TAL1, ALAS2, AHSP, BCL11A, ZNF160*
Term	**GenesUpregulatedintheTMGroup**
DefenseResponse	*OAS1, CCL4L1, CXCL10, MICA, CASP5, FPR2, IFIT3, IL1B, LILRB2,* METRNL, PTPN2, TLR4,VNN1
Response to External Stimuli	*CCL4L1, CXCL10, MICA, ATF3, BATF3, CASP5, FPR2, IFIT3, IL1B,* LILRB2, METRNL, KCNJ2, PTPN2, TLR4
InflammatoryResponse	*CCL4L1, CXCL10, FPR2, IL1B, METRNL, PTPN2, TLR4, VNN1*
Immune System Processes	*OAS1, CCL4L1, CXCL10, FCGR3B, MICA, FPR2, IFIT3, IL1B,* LILRB2, PTPN2, TLR4, VNN1
HomeostaticProcesses	*CXCL10, CKB, FPR2, IL1B, METRNL, KCNJ2, PTPN2, SLC31A2,* SL4A8, TLR4, UTS2
CellChemotaxis	GPR44, CCRL2, FPR2, CXCL10

- **Gene Classification Based on Associated Disease**

  Groupings of differentially expressed genes based on associated diseases are shown in Table 4. 62 genes were linked to hematologic diseases, 26 genes to coronary artery disease, 34 genes to diabetes complications, 49 genes to inflammation, and 64 genes to cardiovascular diseases. All thementionnedgenes that are related to diseases have been downregulated in the TM group compared to the control group (Table 04).

Table 04. *Differentially Expressed Genes Classified According to Associated Diseases (All Downregulated in the TM Group Relative to Control Group).*

Disease	Genes
HematologicDiseases	*TRIM10, VPREB3, CFH, MGP, F2RL3, AHSP, TAL1, ITGB3, HBD, GATM, HRASLS, TMCC2, OSBP2, TNFRSF13C, PTCRA, DMTN, GP9, TNS1, CAV1, JAM3, CMTM5, BCL11A, SOCS3, SNCA, HBA2, SH2D3C, PTPRN, NR1I2, TGFB1I1, HDC, HBM, DDX11, PAWR, ITGB5, LMNA, ITGA2B, CABP5, THBS1, FOXP4, HBA1, ANK1, GP5, MAP1A, SLC35D3, CALD1, CD22, SLC4A1, BCR, LAMC1, ALOX12, HOMER2, TREML1, ALAS2, CA1, ABCB4, XK, EBF1, PTPRF, MMRN1, PLOD2, VWF, GP6*
CoronaryArteryDisease	*CFH, MGP, F2RL3, ITGB3, MGLL, TNFRSF13C, CAV1, JAM3, SOCS3,PNOC, FSTL1, NDUFAF3, NR1I2, LMNA, ITGA2B, THBS1, HBA1,GP5,CALD1, PEAR1, EBF1, PTPRF, SLC6A4, VWF, GP6, FHL1*
Diabetes Complications	*CFH, MGP, F2RL3, ITGB3, GATM, SGCE, DMTN, CAV1, SOCS3, PNOC, FSTL1, HBA2, NDUFAF3, PTPRN, TGFB1I1, HDC, CNTNAP2, LMNA, ITGA2B, THBS1, SELENBP1, HBA1, ANK1, GP5, CALD1, CD22, SLC4A1, LAMC1, ALOX12, CA1, PTPRF, SLC6A4, VWF, GP6*
Inflammation	*CFH, MGP, CTDSPL, F2RL3, TAL1, ITGB3, MGLL, GATM, HRASLS, SLC8A3, TNFRSF13C, DMTN, WNT7A, GP9, CAV1, JAM3, SOCS3, SNCA, PNOC,FSTL1, HBA2, SH2D3C, PTPRN, NR1I2, HDC, PAWR, ITGB5, LMNA, ITGA2B, THBS1, SELENBP1, HBA1, ANK1, GP5, MAP1A, CALD1, CD22, SLC4A1, BCR, ALOX12, TREML1, ALAS2, CA1, ABCB4, EBF1, PTPRF, SLC6A4, MMRN1, VWF*
CardiovascularDisease	*VPREB3, CFH, MGP, CTDSPL, F2RL3, AHSP, TAL1, ITGB3, HBD,MGLL, GATM, HRASLS, SGCE, SLC8A3, TNFRSF13C, DMTN, WNT7A,GP9, CAV1, JAM3, CMTM5, SOCS3, SNCA, PNOC, FSTL1, HBA2, NDUFAF3, PTPRN, NR1I2, TGFB1I1, HDC, DDX11, PAWR, CNTNAP2, ITGB5, LMNA, ITGA2B, THBS1, SELENBP1, FOXP4, HBA1, ANK1, GP5, MAP1A, CALD1, CD22, SLC4A1, BCR, LAMC1, ALOX12, PEAR1, ALAS2, CA1, ABCB4, XK, EBF1, PTPRF, SLC6A4, MMRN1, PLOD2, ZNF160, VWF, GP6, FHL1*

Discussion:

Indications that the TM group expresses a low-inflammation trait come from the individual genes. The pro-inflammatory genes in Network 1 were direct (for example, SOCS3) and indirect (for example, ITGB3) target genes of NF-κB. Expression of suppression of signaling cytokine 3 (SOCS3) isknown to be in direct association with pro-inflammatory cytokine levels (Chaves de Souza, J.A, and Al, 2013)[49], as well as expression levels of integrin genes (ITGB3, ITGB5, and ITGA2B) (Kuparinen et al., 2013).Relative down-regulation of these genes and 45 others linked to inflammatory disease was found in the TM group.

Based on the up-regulation of genes related to disease resistance, for example, those in the defense response and immune system addresses categories of analysis of the term enrichment of ontological processes of genes.

This conclusion is supported by the differentiated roles of specific genes. For example, 5 genes are primarily associated with anticancer activity (CXCL10, MICA, FPR2, CASP5 and CASP7),three genes associated with both anticancer and anti-microbial action (OAS1, ATF3 and IFIT3),and four genes which are principally associated with the defensive response to viruses and bacteria (CCL4L1, IL1B, ANKRD22 and TLR4).This result for the genes put in place in the TM group.

This is consistent with earlier findings from short-term and long-term meditation studies. A practice where the TM program reduces the effects of stress well below the level observed in the general population. (Nidich, S.I,et Al,2009 ;MacLean, C.R,et al.,1997 ;Walton, K.G.et al,1995).

Other evidence connecting stress effects with inflammation and disease is found in the relationship between genes grouped through ontological process term enrichment and genes grouped through disease association analysis. Using the ontological gene enrichment, 35 different expressed genes were classified as being related to "stress response."Of these 35 genes, 27 were also identified among the 49 genes classified as inflammation by disease association analysis.

Predictably, the larger, less well-matched groups of TM and control participants in which 15 key genes were studied by qPCR showed fewer statistically significant expression differences than when comparing the microarrays of well-matched groups. However, for

each of the main areas discussed, the differential expression of one or more key genes became important.

As a result, the results for SOCS3 and ITGB5 confirmed an anti-inflammatory condition, results for SOCS3 and AHSP verified the state of enhanced energy efficiency, and the outcome for CXCL10 (tumor suppressor) confirmed a higher defensive response in the meditation group.

It is expected that qPCR data on a larger sample of the 200 genes in the discovery stage will further confirm these results.

III.8. The impact of different MBI's in different population types on the regulation of the immune system and reducing inflammation (Buric and colleagues, 2017)

Results:

The results of the different 18 articles studied in this review, observed that there is 81% of studies had a reduction in inflammation related genes and/or transcription factors such NF-κB−, CREB−, TNF, TLR4 and an increase in IRF and GR, thus the related genes toapoptosis, Cell metabolism,inflammation, resulting in an increase of Immune regulation.

Discussion:

According to 18 studies in the review article of Buric and colleagues, and despite the small effect sizes of most genes, MBIs counteract the impact of stress on the immune system, a general pattern emerges: pro-inflammatory genes and pathways get downregulated. A significant downregulation was found in other studies. In exceptions, two uncontrolled trials measured the immediate effects of MBIs in experienced practitioners, which is probably the consequence of the sample sizes of 10 and 2 (Ravnik-GlavačM,et al ,2012 ;Qu S,et al,2013), the norm being that 15 participants per group provide statistical power greater than 80% for the gene expression outcome (Creswell JD,et al,2012 ; Black DS,et al,20012). A further exception was one controlled trial that compared 19 long-term practitioners to 20 short-term practitioners of RR and did not detect changes in inflammatory pathways (DusekJA,et al,2008). This could be due to the different methods of gene expression detection and analysis. Therefore, the results suggest that the various psychological and physiological benefits of MBIs may be mediated through the

downregulation of pro-inflammatory genes and pathways. However, to show the level of effectiveness of MBIs on these genetic expression changes, we need to address the severe limitations of the reviewed studies (Buric et al., 2017).

An active control group that carefully mirror the MBIs (e.g., length of time, meaningfulness of the practice) should be a mandatory procedure in studies of gene expression analysis with behavioral interventions aimed at taking into account the many nonspecific effects of MBIs.. In a study, both the meditation and the relaxation control group practiced at home in similar conditions (audio CD of the same length of time ; eyes closed). The effects of MBIs depend on the amount of regular practice. Two studies (Creswell JD,et al,2012 ;Bower JE,et,Al,2015) found that some biological results became significant, when those individuals that practiced regularly were analyzed separately. It is important that future studies measure the frequency of practice and include dosage-related effects in addition to the overall effects of MBIs on gene expression.

Furthermore ; biological outcomes of two other studies (Creswell JD ,et al,2012 ;KalimanP,et al,2014) attempted to find associations between gene expression changes and psychological constructs, such as stress reactivity and loneliness. In a study, two groups of healthy and stressed adults tested sitting meditation at home and moving in groups from 4 days to 4 months ; the results presented Considerable variation.

Some aspects needs to bear in mind in the reviewed studies, including differents varieties of gene expression patterns and functions in peripheral blood mononuclear cells (PBMCs), that could affect data interpretation by showing mixed gene expression emerged (TOA). And lack of biological consequences of the observed gene expression changes, because 38% of studies that employed circulating proteins (e.g., CRP, interleukins, or cortisol) measured at least one inflammatory protein and the results were non-significant in 76% of cases.

The assessment of inflammation was taken in consideration as well. If one per 11 single inflammatory measure has decreased after an intervention, cannot confirm that the immune system is enhanced.

Therefore, in the aim of validating the connections between genetic and other data and supporting the consistent evidence for the benefits of these techniques (Farias M,et al,2016). More researchs must be done. Besides, isolating PMBC subtypes before and after

MBIs would be a great progress in epigenetic to demonstrate the different responses in vitro in future studies.

In the study of Loucks and colleagues and yang and colleagues we will discuss more deeply the association of MBI's and diabetes, which we've choosen it as a disease example to know how does MBI's act on it (Loucks et al., 2016 ; Yang et al., 2021).

III.9. The impact of mindfulness on diabetes and blood glucose regulation (Loucks and colleagues, 2016)

Results:

There's other unadjusted analyses that have shown significant associations of diabetes status with childhood socio-economic index, obesity, high blood pressure, HDL cholesterol, family history of diabetes, sense of control, and educational attainment.Multivariable regression analyses showed that participants with type 2 diabetes as a dependent variable exhibited similar trends., but the outcome estimates were not statistically significant, where participants with high or low MAAS were less likely to have type 2 diabetes, after adjusting for age, sex, race/ethnicity, family history of diabetes, and childhood SES. The total effect of high or low MAAS on fasting blood glucose in comprehensive mediation assays was a prevalence ratio of adjusted based on age, race or ethnic origin, sex, family history of diabetes and childhood SES (Loucks et al., 2016).

Discussion:

For the study of Loucks and colleagues, the results of the study showed that participants with higher dispositional mindfulness were significantly more likely to have normal blood glucose. After adjustment for age, race/ethnic origin, gender, family history of diabetes and child SES.

The mediating analyses between mindfulness and glucose regulation suggested potential mediating roles for obesity and a sense of control.

The underlying mechanisms in Mindful awareness of experiences of overconsumption of food and inappropriate physical activity can help participants be aware of the long range of their immediate food.and make decisions about their long-term wellbeing, Studies have demonstrated from the start that mindfulness is related to a better sense of control and self-

efficacy.For example, a mindful eating intervention in participants with type 2 diabetes showed an improvement in post-intervention dietary self-efficacy.

A prospective study found that participants with more mindfulness of disposition were more likely to adopt their intentions for physical activity than those with less mindfulness of disposition.

A study conducted by our group has demonstrated that control is an important mediator between mindfulness and cardiovascular health.

There's some strengths and limitations for this study, So the dispositional mindfulness was assessed using a self-report questionnaire. Mindfulness assessment is not a standard of excellence, and there is currently a debate around the accuracy of self-reported mindfulness, including the use of MAAS. Results should be interpreted with the knowledge that total effect analyses were performed on the multiply imputed data, which reduce bias due to observed covariates, whereas the mediation analyses were performed using complete case data due to mediation methods not currently available for multiply imputed data.

This study showed an important connection between the mindfulness of the disposition and the regulation of glucose, and new evidence that obesity and a sense of control can act as potential mediators for this risk of diabetes. A variable to improve prevention and treatment of diabetes.

III.10. Epigenetic Changes Induced by Mind–Body Intervention and Their Effects on Diabetes (Yang and colleagues, 2021)

Results:

In the review study of Yang and colleagues, the results obtained in the included studies had a significant decrease in HDL, FBG, HbA1c, PPBG, TC, LDL-C, TG, HDL-C and increased INS. Morefurther there's differentiallyMethylated Area (Yang et al., 2021):

- Fatty acid metabolism: ACADM, CPT1A,HSD17B4
- RNA transport: SAP18, EIF1B, NCBP2
- DNA repair: APITD1, ERCC1
- Glucose homeostasis,stress response,inflammation: KLF15

- DNA damage,immunity,inflammatoryresponses: EGR1
- DNA damage,immunity,hematopoiesis,expression regulationof anti-inflammatorymolecules such as IL-10and COX-2: SP3
- Inflammatory andneuropathicpersistentpain states, dendritepatterning,neurotransmission: SP4
- Involved in immunityandinflammatoryprocesses, as well asvarious neuropathies: EGR2
- Glucose homeostasis: Meis3, Mafk
- Lipid metabolism: APOB, APOC2, HRH1,PTCH1, CLEC11A,NCOR
- Inflammation: TNFa, NF-kB, Nrf2
- Stress-related pathway(glucocorticoid receptor regulation): FKBP5

Discussion:

In this study, we are discussing the following data :

Impact of Mind–Body Intervention on Diabetes

Studies that meta-analyzed the effectiveness of MBI on patients with diabetes revealed a consistent efficacy in blood glucose control and lipid metabolism, albeit with some differences in results.

Impact of Moving Meditation on Diabetes

Many studies showed that exercise meditations, like tai chi, qigong and yoga are efficacious and helpful managing blood sugar in individuals presenting type 2 diabetes (Meng, D et al. 2018 ; Xia, T.W et al., 2019 ; Cui, J et al., 2017 ; Liu, X et al., 2010). A meta-analysis of 21 studies of moving meditation in people with type 2 diabetes found that this meditation considerably increased FBG, postprandial blood glucose(PPBG), HbA1c, low-density lipoprotein cholesterol (LDL-C),total cholesterol (TC), and high-density lipoprotein cholesterol (HDL-C), but by opposition it didn’t increase BMI in comparison with controls groups (Xia, T et al., 2020).

Impact of Tai Chi practice on Diabetes

A systematic meta-analysis of 17 studies on the use of tai chi in people with type 2 diabetes found that tai chi significantly reduced FBG, HbA1c, TC, triglycerides, and BMI, but not LDL-C and HDL in comparison with the control group (Xia, T.W et al., 2019).

A further study (a meta-analysis including 14 studies) examining the effectiveness of tai chi in people with type 2 diabetes found that tai chi reduced FBG, HbA1c, and PPBG compared with the non-exercise control groups (Chao, M et al., 2018).

The common point to both meta-analyses was that Tai Chi reduced FBG and HbA1c in patients with type 2 diabetes.

Impact of Qigong practice on Diabetes

A meta-analysis of 21 randomized controlled trials (RCTs) examining the effects of qigong in adults with type 2 diabetes found that qigong significantly reduced HbA1c, FBG, and PPBG (Meng, D et al., 2018). Another meta-analysis study (11 RCTs) about the efficacy of qigong in adults with T2D, qigong considerably decreased PPBG, FBG, TG, HbA1c, and HDL-C, but in TC and LDL-C no significant change was seen with respect to (Yang, H. ; Wu, X. ; Wang, M., 2018). The common observation in those meta-analyses is that qi gong lowered the FBG, HbA1c, and PPBG in the T2D patients.

Impact of Yoga practice on Diabetes

A meta-analysis of 12 RCTs examining the effects of yoga in adults with type 2 diabetes found that yoga considerably lowered FBG, HbA1c, PPBG, TC, HDL-C, and LDL-C, but not TG. Yan, LM ; Pan, L ; Le, JJ ; Guo, YZ, 2017). A second meta-analysis study examining the yoga efficacity in adults with type 2 diabetes (a meta-analysis based on 23 studies) found that yoga enhanced HbA1c, FBG, and PPBG compared to the control group. Moreover, yoga significantly improved other risk factors, such as lipid profile, blood pressure, BMI, waist–hip ratio, and cortisol level (Thind, H. ;Lantini, R. ; Balletto, B.L. ; Donahue, M.L. ; Salmoirago-Blotcher, E. ; Bock, B.C. ; Scott-Sheldon, L.A.J, 2017). In a meta-analysis using 17 RCTs regarding the effects of yoga in adults with T2D, yoga improved HbA1c, FBG, and PPBG compared with control groups (Kumar, V. ; Jagannathan, A. ; Philip, M. ; Thulasi, A. ; Angadi, P. ; Raghuram, N, 2016). Thus, It has been reported by all those three meta-analyses examining the effects of yoga in patients presenting type 2 diabetes, that yoga decreased FBG, HbA1c, and PPBG. A meta-analysis comprising 42 RCTs examined the effectiveness of yoga (MBSR) against active controls in

all populations, and reported a significant reduction in FBG, TC, and LDL-C, with unchanged TG and HDL-C (Pascoe, M.C. ; Thompson, D.R. ; Ski, C.F, 2017). Lower blood sugar levels were consistently observed in the yoga group, regardless of the group studied.

Mindfulness practice

A meta-analysis of eight RCTs conducted in people with diabetes (including type 1 and type 2) found that MBI had beneficial effects on HbA1c, diabetes distress, stress and depression (Ni, Y. ; Ma, L. ; Li, J, 2020). The fact that MBI positively affects HbA1c is consistent with previous meta- analyses (Harkness, E. ; Macdonald, W. ; Valderas, J. ; Coventry, P. ; Gask, L. ; Bower, P, 2010 ; Ismail, K. ; Winkley, K. ; Rabe-Hesketh, S, 2004). Another study, a meta-analysis of nine RCTs in people with diabetes (including type 1 and type 2), found that MBSR and mindful cognitive therapy (MBCT) improved depression, the mental health composite score of QOL, and HbA1c (Ni, Y, Ma) were found to be reduced., L, Li, J, 2020). The analyzes sensitivity analyzes suggested that the effect of MBSR or MBCT on HbA1c disappeared when long-term follow-up studies (>6 months) were eliminated, suggesting that MBSR or MBCT effects on HbA1c are delayed.

Potential Mechanism for Diabetes-Related Effects of Mind–Body Intervention

Studies in rodents have observed that parental stress, fetal stress, and postnatal adversity affect epigenetic modifications of the glucocorticoid receptor promoter. As stressed individuals become adults, the resulting epigenetic changes can influence coping behavior under adverse conditions, and this behavioral pattern can be transmitted across generations.

Although, it has been noted that these transgenerational epigenetic traits can be reversed by environmental wealth, including favorable experiences, and that environmental wealth can be a powerful intervention to reverse epigenetic programming.

(Gapp, K et al.,2016 ; McCreary J.K et al.,2016). The environmental abundance used in the above studies is a stimulation not only cognitive but also somatosensory,exercise, and visual stimuli. For humans, MBI uses breathing to be aware of the present moment and the state of one’s body, and gentle, slow movements improve the body-brain connection.

Consequently, MBI provides components that correspond to environmental abundance. Indeed, MBI changes epigenetic modifications, as well as mental and physical functions as follows (Venditti, S et al,.2020 ;Chaix, R et al,.2020).

Epigenetics alterations linked to Glucose/Lipid Metabolism and Inflammation through MBI's

MBI-induced epigenetic changes reported so far include DNA methylation (Chaix, R et al,.2020 ; Ren, H et al., 2012) and histone modification (Kaliman, P et al.,2014), besides there are currently no reports of noncoding RNAs. However, the collected research results show that MBI positively improves blood glucose levels and blood lipids in diabetic patients. To investigate how mindfulness affects epigenetic pathways, García-Campayo et al had done a comparison of the methylation profiles from the circulating lymphocytes of non-meditators and experienced meditators (with more than 10 years of experience). They detected 64 differentially methylated regions containing 43 genes that were associated with the regulation of glucose homeostasis, lipid metabolism, protein folding, neurotransmission, and inflammatory pathways. (García-Campayo et al., 2018). The majority of these genes are associated with neurological disorders, psychiatric disorders, cardiovascular disease, and cancer. In silico analysis suggests that epigenetic responses to mindfulness practices regulate inflammatory pathways dependent on the tumor necrosis factor (TNF) alpha and nuclear factor kappa light chain enhancer signaling from activated B cells (NF-kB).

The authors completed GO (Gene Ontology) enrichment evaluation to represent the capabilities of genes which have greater mindfulness-associated differentially methylated regions (DMRs). In the mobile factor category, numerous GO phrases had been associated with unique lipoprotein particles, in which because the maximum strongly associated GO time period turned into phospholipase binding in molecular feature category.

In between the differentially methylated genes were several genes that function in lipid metabolism or related functions (e.g. APOB, APOC2, HRH1, PTCH1, CLEC11A, NCOR). In the midst of the different genes, the most frequently represented top canonical pathways are LXR/RXR and FXR/RXR, that are essential pathways in atherosclerotic signaling and regulation of cholesterol, fatty acid, and glucose homeostasis. In addition, they also contained transcription factor-binding motifs and DMRs enriched in Meis3 or Mak, transcription factors associated with pancreatic beta-cell survival or insulin metabolism. In

response to oxidative stress, transcription factors from different motifs act in concert by directing the upregulation of Nrf2, which exerts anti-inflammatory action and neuroprotective function. The prediction and analysis of the upstream regulators of 43 differentially methylated genes by meditation found the cytokine TNF to be the most highly correlated. TNF is a cytokine that has been implicated in a variety of human diseases, and previous studies have linked meditation to TNF (Elsenbruch, S et al., 2005 ; Rosenkranz M.A et al., 2013).

Garcia's study (García-Campayo et al., 2018) analyzed DNA methylation in peripheral blood mononuclear cells compared with meditation-naïve controls and found that meditators were associated with glucose and lipid metabolism and inflammation. We show changes in epigenetic traits, suggesting associated functional improvements by MBI., supports the potential use of MBI to improve glucose and lipid metabolism and inflammatory function. In a study which analyzed the same DNA samples, the SERPINB9 gene, which is differentially methylated by meditation (Mendioroz, M. ; Puebla-Guedea, M. ; Montero-Marín, J. ; Urdánoz-Casado, A. ; Blanco-Luquin, I. ; Roldán, M. ; Labarga, A. ; García-Campayo, J, 2020), has been known to be associated with inflammation and insulin resistance in coronary atherosclerosis (Fritsch, K. ; Finke, J. ; Grüllich, C, 2013).

Psychological Stress reduction through MBI's

MBI has been shown to be effective in reducing negative psychological factors such as depression. A meta-analysis of 38 of his RCTs examining the effects of meditation on a health care worker and her MBI found that the intervention significantly reduced anxiety, depression, emotional distress, and stress and improved overall well-being (Spinelli et al., 2019). A meta-analysis of 6 clinical studies involving 405 pregnant women revealed that yoga-based interventions significantly decreased depression during pregnancy (Ng, Q.X et al,2019). In addition, a meta-analysis examining the effects of qigong and tai chi on cancer survivors found that the intervention was significantly associated with fatigue symptoms, sleep quality, and positive trends. Was found to be effective for, but not statistically effective on anxiety, stress, depressive symptoms, or quality of life (Zeng et al., 2019).

Thus, it has been investigated whether epigenetic changes occur when MBI has a positive effect on psychological factors.

According to Bishop, J.R et al (2018), they performed a study that could provide an answer to this. They performed MBSR in patients with post-traumatic stress disorder (PTSD) and examined differences in DNA methylation in peripheral blood samples between responders and non-responders to the MBSR intervention. They observed that methylation of her CpGs within the FKBP5 gene region, which contains the glucocorticoid response element, was decreased in responders and increased in non-responders, suggesting that effective meditation correlates stress-related signals at the molecular level, suggesting that it is related to transduction pathways (Bishop J.R et al., 2018).

Regrouped brain imaging studies support reduction of stress, depression, anxiety, and PTSD with MBI. A meta-analysis of 21 neuroimaging studies (300 meditation practitioners) found consistent alterations in eight brain regions in meditators, regardless of meditation method. Among these regions, the orbitofrontal cortex and anterior and mid cingulate were specifically associated with self and emotion regulation (Fox, K.C et al, 2014). Therefore, MBI changes the brain structures and allows heightened self-monitoring and a better emotional regulation. These structural changes of the brain caused by MBI explain how MBI brings apparent beneficial effects on depression, anxiety, and stress.

Specifically, psychological stress is a predictor of T2D development and a prognostic factor for ongoing T2D (Hackett et al,2017). Because the effect of MBI to reduce psychological stress has been proven, it might also help in reducing the T2D risk induced through psychological stress. Because stress changes the neuroendocrine (cortisol), inflammatory, and autonomic neural pathways (Hackett et al,2017), it is of interest to ascertain how MBI, which effectively relieves stress and controls blood glucose, alters each of these pathways.

Cortisol Secretion and Glycemic Control through MBI's

Cortisol affects glucose homeostasis (Dallman, M.F et al, 1993). Its circulation induces the release of glucose and lipids (Hackett et al,2017). In particular, diabetic patients had elevated evening cortisol. MBI may alter her HPA axis and control blood glucose through regulation of cortisol secretion, a consequence of the HPA axis.A meta-analysis of 42 RCTs examining the effects of yoga asanas with and without MBSR on stress-related physiological measures in all populations, the practice of yoga appears to reduce waking, as well as afternoon and evening salivary cortisol (Pascoe et ,2017). Additionally, a meta-

analysis of 23 studies examining the effects of yoga in people with type 2 diabetes found that yoga significantly reduced afternoon, evening, and waking cortisol levels but did not reduce the 30- or 60-min post-waking and mid-morning cortisol levels,or the cortisol slope (Thind, H et al, 2017). According to a meta-analysis related to qigong, the cortisol level was not significantly changed (So, W.W.Y et al,2019). Therefore, blood glucose levels altered by MBI may be partially due to a cortisol-mediated pathway.

Autonomic Nervous System Changes and Glycemic Control through Mind–Body Intervention

Elevated blood pressure is a known risk factor for diabetes. A meta-analysis of prospective studies found that elevated blood pressure was associated with an increased risk of diabetes (Emdin et al., 2015). Studies have shown that MBI is effective in lowering blood pressure. In a meta-analysis of nine studies examining the effects of TM on blood pressure in adults with hypertension or cardiovascular disease, within-group analysis found that in systole and diastole blood pressures were significantly reduced through the intervention (Gathright et al., 2019). A meta-analysis analyzed 49 studies on the effects of yoga in obese middle-aged adults with hypertension, yoga significantly reduced both systolic and diastolic blood pressures compared with the controls (Wu, Y et al., 2019). Another meta- analysis of 13 studies on meditation and yoga revealed that these interventions reduced both systolic and diastolic blood pressures (Park, S.H et al., 2017). Thus, the reduction in blood pressure with MBI appeared to partially contribute to the reduced risk of diabetes.

Inflammation Reduction and Glycemic Control through Mind–Body Intervention

Inflammation is a factor that increases the risk of T2D (Donath, M.Y et al.,2011 ; Wang, X. ; et al, 2013). A lot of studies have reported a reduction in inflammatory markers with MBI. In a study that systematically reviewed 20 of his RCTs on mindfulness meditation, NF-kB transcriptional activity and CRP levels were decreased in mindfulness meditation practitioners compared with the general population,suggesting that inflammation was decreased (Black, D.S. ;Slavich, G.M, 2016). A single 8-h period of intensive mindfulness meditation significantly reduced the expression of histone deacetylase genes (HDAC2,3,9) and reduced global histone modifications (H4ac ; H3K4 me3). Altered and decreased expression of pro-inflammatory genes (RIPK2, COX2).) Comparison of Peripheral Blood Samples of Meditation Professionals and Beginner Meditation Practitioners Who Participated in an 8-Hour Recreational Activity. (Kaliman al., 2014), there by indicating

that an MBI-induced reduction of pro- inflammatory gene expression occurs along with epigenetic alterations within a day in MBI experts. In a meta-analysis of 34 RCT studies (2219 participants) that examined measures of immune outcome altered by MBI (tai chi, qigong, meditation, yoga), MBI significantly reduced CRP levels, whereas IL-6 and TNF-alpha levels were not significantly altered (Morgan, N et al., 2014). Additionally, yoga and mindfulness practices have been reported to decrease the expression of pro-inflammatory genes in blood cells.(Creswell J.D et al., 2012 ; Black D.S et al., 2013). A study comparing between a yoga group with a control group in women reporting emotional distress showed that the yoga group had lower methylation levels of the TNF gene associated with inflammation than in the control group in peripheral blood samples (Harkess, K.N et al., 2016). Strikingly, decreased methylation of the TNF-α gene promoter in blood mononuclear cell DNA is associated with weight loss in obese men also with the reduction of circulating levels of baseline TNF-alpha (Campion et al.,2009). Since inflammation is a factor that increases the risk of type 2 diabetes, reducing the expression of pro-inflammatory factors by MBI may reduce inflammation, thereby reducing the risk of type 2 diabetes.

Delayed Epigenetic Age through Mind–Body Intervention and Its Relation to Type 2 Diabetes

Studies have revealed that biological aging measurements are possible by analyzing the methylation of CpG sites in the genome (Horvath, S, 2013 ; Hannum G., 2013). Deterioration of important genome maintenance mechanisms might occur due to aging, resulting in changes in DNA methylation over time. The results of study in this field thus far suggest that MBI might potentially retard or inverse aging associated modification in the epigenome. Chaix and colleagues (Chaix et al., 2017) observed that the aging rate was significantly higher in people above 52 years of age than those below 52 years of age in the control group.

However, no epigenetic age difference between these two different chronological ages has been observed in experienced meditators. Additionally, the epigenetic aging in meditators was highly decreased relatively to the duration of meditation. This finding suggested that incorporating meditation into daily routines might slow the epigenetic clock, giving potential health benefits in the long run (Chaix, R. Et al.,2017). Following this study, we found that a brief meditation intervention (8 hours) by an experienced meditator can

rapidly affect the methylome of genes associated with immune metabolism, inflammation, and aging. (Chaix, R et al., 2020).

A recently reported study by Mendioroz et al (Mendioroz, M et al,2020) Investigated 14 differentially methylated regions in peripheral blood samples, present in the subtelomeric region, which were identified in long-term meditators compared with the controls in their previous work (García-Campayo et al,2018). The telomere length in long-term meditators was positively correlated with the methylation level of the GPR31 gene, but inversely correlated with the methylation level of the SERPINB9 gene. In addition, the correlation between telomere length and age that was observed in the general population was no longer found in long-term meditators.

These results therefore suggest that long-term meditation may be associated with epigenetic mechanisms associated with specific gene-specific DNA methylation changes at specific subtelomeric regions. Increase. Moreover, delays in epigenetic aging rates were demonstrated in the analysis of epigenetic effects of tai chi, a moving meditation (Ren, H et al,2012). Approximately 66 methylation sites of experienced tai chi performers and the general population were compared using their saliva sample, and a significant difference was found in 6 CpG sites of 3 different chromosomes. Methylation changes in this area relative to age were significantly slower in the tai chi cohort compared to that of the control cohort (Ren, H et al, 2012).

Because this research field is relatively new, several studies have been performed using a cross-sectional design or with a small number of people ; therefore, more research should be performed to demonstrate a causal relationship between MBI and DNA methylation. It is generally well-known that fasting glucose levels increase as age increases (Yi, S.W et al, 2017 ;Qiao, Q. ; et al, 2003). Therefore, the delay of aging rates by epigenetic marks of aging-related genes through MBI (Chaix, R et al, 2003 ;Chaix, R et al,2017 ; Ren, H et al,2012) might partly contribute to the effect of MBI on reduction of blood glucose.

Below, the Figure 10 summerize all what could cause the dibete and how the MBI's affectit

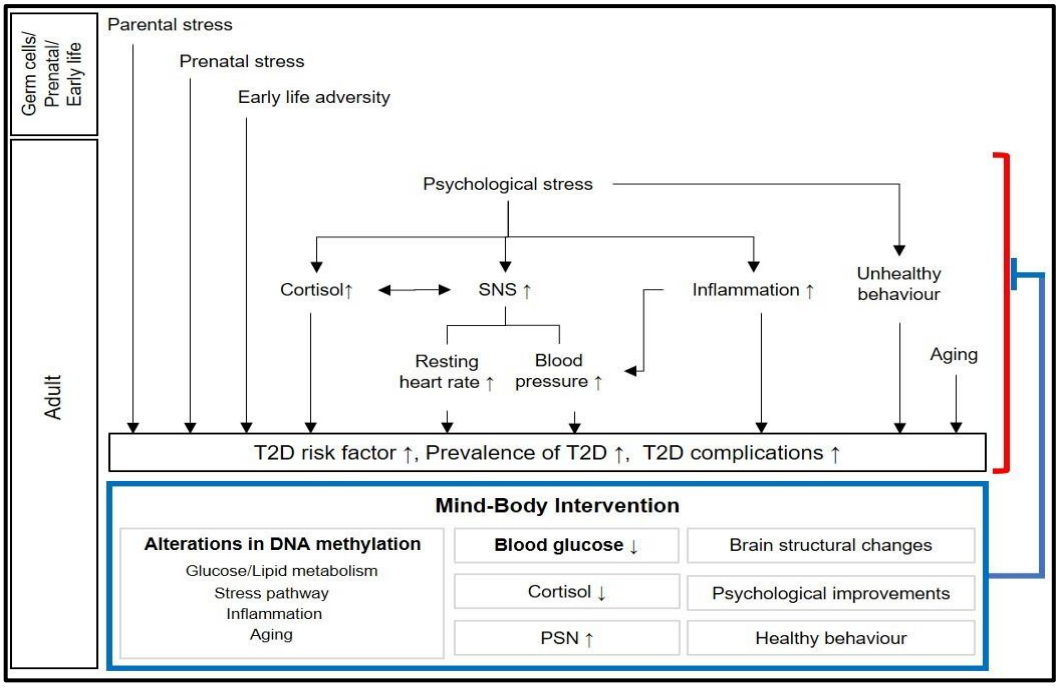

Figure13:*Potential causes contributing to diabetes (red) and mind–body intervention-induced beneficial changes including altered epigenetic modification (blue).*

Abbreviations: SNS, sympathetic nervous system; T2D, type 2 diabetes; PSN, parasympathetic nervous system; ↑, increased; ↓, reduced.

III.11. General discussion

After studying the totality of those articles we can say that there's some existing evidence which shwos that the many and multiple mind body interventions do have an impact on the molecular level inducing changes in the right direction.

This study demonstrates that meditation and its related practices do appear to have epigenetic impacts, hence giving us good reason to investigate the biological mechanism by which meditation can exert its purported effects.

The most significant group of genes were pro-inflammatory mediators that are linked to the NF-κB pathway which is involved in the inflammatory stress response. In most studies,

genes coding for pro-inflammatory mediators were down regulated significantly. These studies included several types of meditation practices.

Studies highlighted that psychological stress induces inflammation through the actions of pro-inflammatory mediators which are under the regulation of the NF-κB pathway. Furthermore, it has been well established that a range of psychiatric illnesses, specifically clinical depression, have been linked with the chronic inflammatory state. The current evidence that meditation and related practices decrease the expression of genes relating to the NF-κB pathway highlights its potential as a treatment for psychiatric illnesses and also as a method of promoting general wellbeing.

Therefore, we've seen that going from stress to inflammation may also be a risk factor for diabetes as much as the factor of aging too, and other factors such as personality traits and behaviors, where the evidence stands for related mind body interventions which regulates all the mentioned factors following by blood glucose regulation.

Also, it has been demonstrated that meditation and related practices do have an influence on TA and TL, where they show the evidence of an increased TA and TL after an intervention. But consequently, from our point of we think that those researchers need to multiply their trials and experiments on larger samples, more diversified populations and different durations including more type of related mind body interventions, in order to confirm the evidence that it is suitable for everyone or at least most of the population and to identify which MBI type is more effective with specifying it's effect.

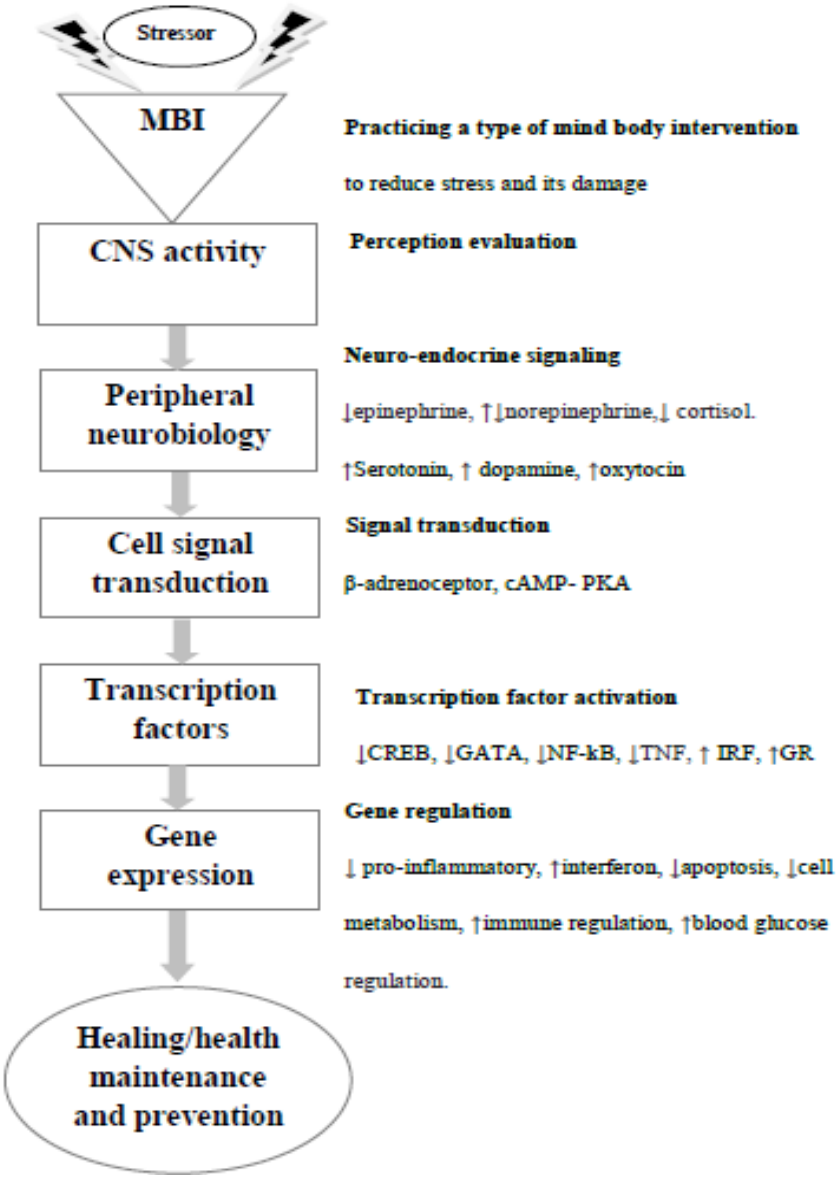

Figure14:*This figure shows the cascade of the mechanism that occurs when practicing MBI's after a threat or a stress exposure.*

After experiencing the feeling of threatening after a stressful situation or thought, we suggest practicing MBI's because of their health benefits that starts with a perception of things positively in a way to feel relaxed which promotes an CNS activity in the brain which follows with a neuro-endocrine signaling for optimizing the secretion of the serotonin, dopamine and oxytocin, after this, there's a cell signal transduction that is emitted (β-adrenoceptor, cAMP- PKA) regulating the expression of transcription factor such as the CREB, GATA, NF-kB and TNF that are reduced, contrary to the IRF and GR that are increased. Which follows up with gene regulation including the genes that are implicated in the pro-inflammatory, interferon, apoptosis, cell metabolism, immune

regulation, blood glucose regulation. And finally, we suggest that all those reactions may provide the healing from the related diseases with stress andmay promote health maintenance, prevention and well being.

CONCLUSION AND IMPLICATIONS FOR THE FUTURE

Conclusion and Implications for the Future

In our study we've found that in the 10articles studied there was a focus on the genetic impacts of the many types of meditation and/or the mind body interventions.

The outcomes of this study provide preliminary evidence that appears to show that different mind body related practices have different biological impacts on the body. This is based on the fact that gene expression changes were found to be relevant when comparing. It is not unreasonable to consider the possibility that the alteration of gene expression changes in the categories of cancer, inflammation and cell structure and function...etc, may lead to different biological outcomes. This might therefore bring about different biological outcomes in different practitioners of different types of meditation or MBI's.

In conclusion, this study clearly suggests that the multiple techniques of meditation with different types and definitions, may well have different epigenetic implications and this supports the idea that was discussed earlier in this thesis that grouping all forms of meditation and MBI's under a single rubric is an inadequate way of understanding the effects of those techniques. Different approaches to meditation (as a more popular term), because they have different biological implications, ought to be clearly distinguished from each other and studied separately. This is supported not only by the gene expression changes that were unique to each group in this study, but also the fact that some of these gene expression changes were different when compared to others.

Additionally, this study also supports the idea that the different types and definitions of meditation and/or MBI's are important to understand.

Those studies should be replicated on a larger scale in order to highlight any subtle between group differences concerning gene expression changes for mind body types interventions. Additionally, future studies would ideally be conducted with greater levels of methodological rigor. This may involve extending the intervention time, increasing the amount of time each participant spends practicing per week and also the confirmation of any significant gene expression changes through quantitative PCR determinations.

In addition, other types of mind body interventions should be assessed in a similar way of design studies which compare different types of meditation and MBI's would allow us to confirm the preliminary idea that different types of meditation and

MBI's have different genetic impacts on the body. Future comparison studies may also shed light on the possibility that due to the different types of mind body related practices having different biological impacts on the body, it is plausible that some of these types may be potentially more beneficial than others.

In order to enhance the validity of future studies it is important to establish a connection between meditation invoked gene expression changes and how these relate to physical and mental health outcomes in the practitioner. Physical and mental health outcomes could include mood, quality of life and mortality (for possible long- term cohort studies). Making deeper researchers on the relationship between these two parameters will help us better understand what benefits are achieved through the alteration of specific genes. Therefore, giving us additional insight on the biological mechanism of action through which mind body interventions acts.

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APPENDIXIES

Appendix 1- Poses and benefits of MBI's

Below we present the poses and benefits of every mind body interventions, such as the meditation, transcedental meditation, yoga, tai chi and qigong.

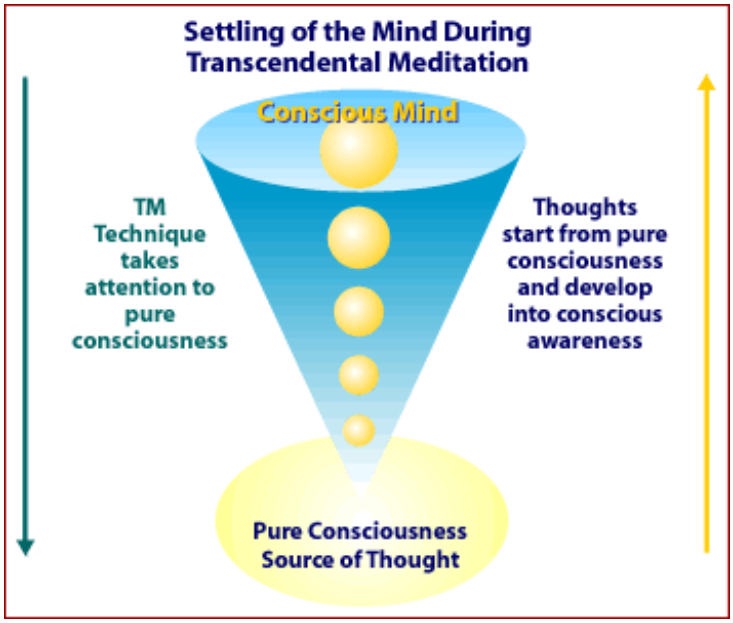

Figure: a figure shwing the basics of how does the TM work

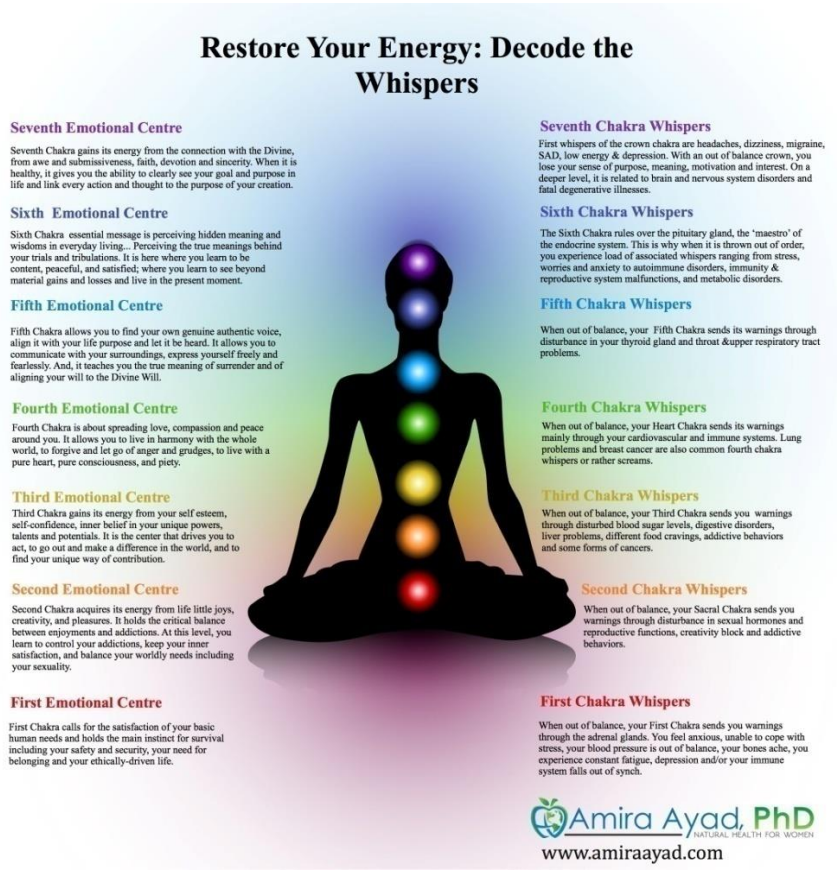

Figure: PhD Ayad explain Chakra energy

Figure: steps to mindfulness

Figure: The practice of qigong benefits

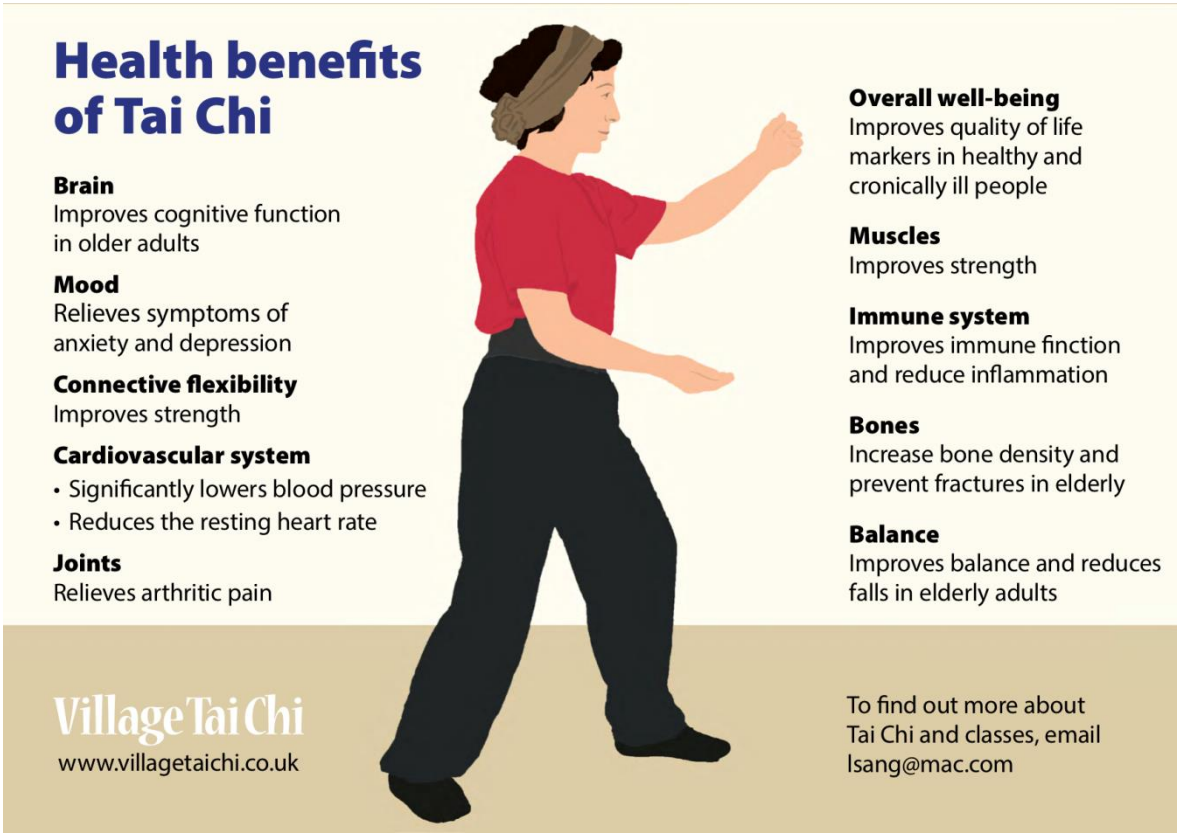

Figure: Tichi health benefits

Appendix 2- Neuroplasticity and MBI's

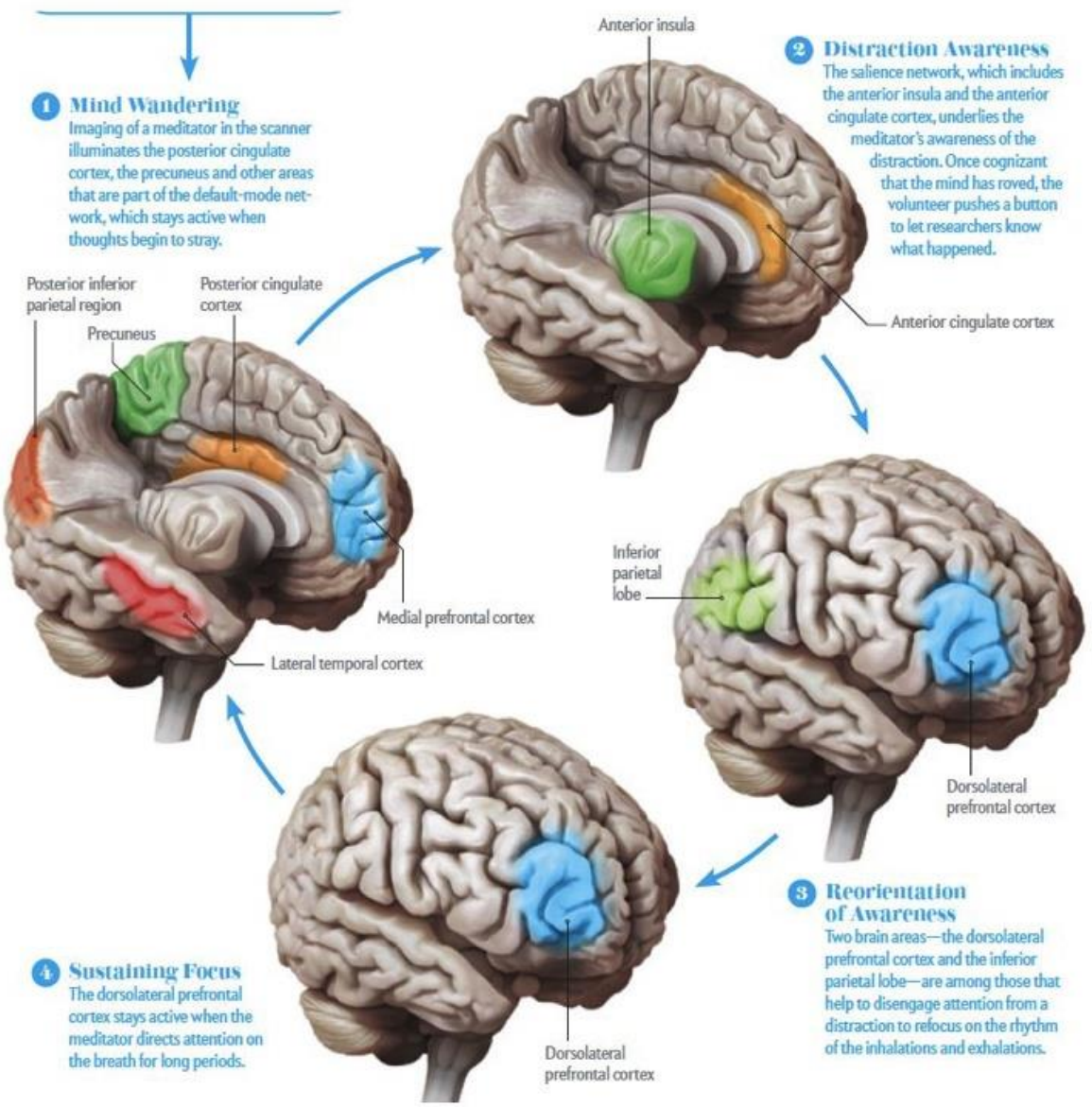

Figure: The effect of the meditation on the brain (neuroplasticity)

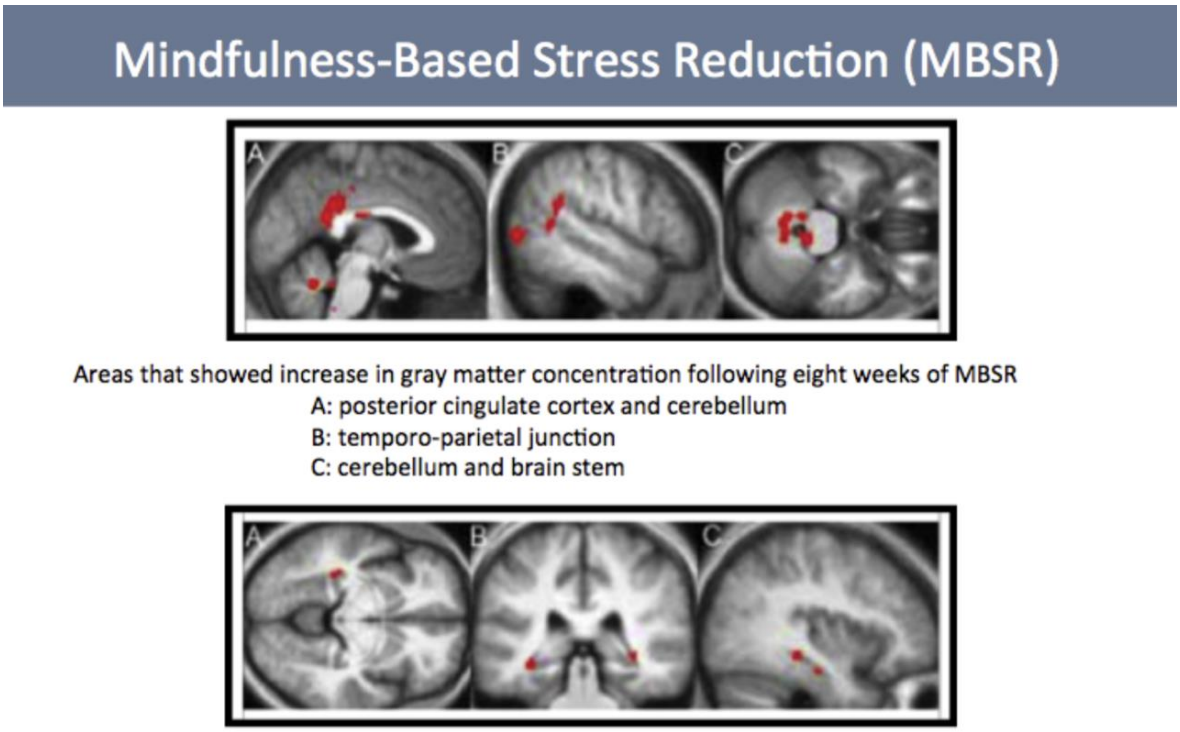

Figure: brain scans of the effect of mindfulness for stress reduction