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Effects of a web-based mindfulness training on brain structure and function

María Guadalupe Mora Álvarez

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Vorsitzende: Prof. Dr. Angela Krackhardt

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Abstract

Mindfulness practice, i.e., the non-judgmental awareness of present-moment experience, has reliably been demonstrated to reduce stress and trait anxiety. Improved attention, altered brain function, changes in white matter, and altered cerebral bloof flow (CBF) have also often been reported, but findings are less consistent. To date, little is known about the relationship between these measures and psychological outcomes. Given the documented detrimental effects of stress and anxiety on cognition and on brain function, I investigated whether stress and anxiety reduction following mindfulness training would be related to improvements in attention, brain activation, changes in CBF and white matter. 42 healthy, meditation-naïve participants (age range: 20 - 60 years old) were randomly allocated to receive either a short (31 days, 15 min/day) online-based mindfulness-training or an active control health information program (matched for structure and time commitment). Participants underwent: a) functional magnetic resonance imaging (fMRI) while completing the attention network test (ANT), b) diffusion tensor imaging (DTI), and c) perfusion imaging at resting-state using arterial spin labeling (ASL). Participants also completed standardized questionnaires on perceived stress, anxiety, physical well-being, mindfulness, and flow experience before and after interventions. Results supported the expected improvement on levels of anxiety. Perceived stress also decreased in the experimental– and not the control group. While no specific effects on any of the three attentional components of the ANT (i.e., alerting, orienting, and executive attention) were found, overall reaction times improved strongly and highly significantly in the experimental, but not the control group. At the neuronal level, no significant training-associated activations were seen during the orienting and executive conditions of the ANT. However, during the ANT alerting condition, brain activation increased in the superior frontal gyrus (SFG), posterior cingulate cortex (PCC), and right hippocampus in the experimental group as a consequence of the mindfulness intervention. While there was no correlation between decreased stress and attentional performance, decreased stress was significantly correlated with activation in the right hippocampus following mindfulness training. Fractional anisotropy (FA) values of white matter in the experimental group increased in the right uncinate fasciculus (UNC), enforcing connections between the right hippocampus and frontal areas of the brain. CBF Results of a region of interest (ROI) analysis on gray matter of core brain regions known to be susceptible to perfusion changes related to mindfulness practices showed a significant decreased in the CBF of the anterior cingulate cortex (ACC) as a result of the web-based mindfulness meditation training; correlations between perceived stress and CBF values showed a less reactive response to stress on the experimental group in this brain region compared to the control group. To conclude, the study provides support that a short online-based mindfulness training have beneficial effects on mental health (i.e., decreased stress and anxiety), attentional performance, and state of mind (i.e., increased flow experience), and it sheds some light on the potential relationship with improved brain function and overall well-being.

Zusammenfassung

Achtsamkeit ist ein Zustand, in dem sich ein Mensch im Hier und Jetzt befindet, dass heiβt, im gegenwärtigen Moment ist, ohne sich Gedanken zu machen oder Wahrnehmungen zu bewerten. Achtsamkeitspraxis kann Stress und Angst zuverlässig reduzieren. Verbesserte Aufmerksamkeit, veränderte Gehirnfunktion, Veränderungen in der weißen Substanz und veränderter zerebraler Blutfluss (cerebral blood flow, engl. CBF) wurden ebenfalls oft in der Literature als ein Effekt von Achtsamkeitsübungen berichtet, allerdings sind diese Ergebnisse weniger eindeutig. Bisher ist wenig über die Beziehung zwischen diesen Maßnahmen und psychologischen Ergebnissen bekannt. Ausgehend von den vielfach dokumentierten schädlichen Auswirkungen von Stress und Angst auf Kognition und Gehirnfunktion habe ich untersucht, ob reduzierte Stress- und Angstwerte nach einem Achtsamkeitstraining mit einer Verbesserung der Aufmerksamkeit, erhöhter Gehirnaktivität, Veränderungen des CBF und der weißen Substanz zusammenhängen. 42 gesunde, meditationsnaive Teilnehmer (Alter: 20 - 60 Jahre) wurden zufällig, zu entweder einem kurzen online-basierten Achtsamkeitstraining (31 Tage, 15 Min/-Tag) oder einem aktiven Kontroll-Gesundheitsinformationsprogramm (in Struktur und Zeitaufwand vergleichbar mit dem Achtsamkeitstraining) zugeteilt. Die Teilnehmer wurden mit den folgenden MRT-Sequenzen gemessen: a) funktioneller Magnetresonanztomographie (fMRT) während der Durchführung des Aufmerksamkeitsnetzwerktests (ANT), b) Diffusions-Tensor-Bildgebung und c) Perfusionsbildgebung im Ruhezustand mittels arteriellem Spin-Labeling (ASL). Zudem füllten die Teilnehmer vor und nach den Interventionen standardisierte Fragebögen zu wahrgenommenem Stress, Angst, körperlichem Wohlbefinden, Achtsamkeit und Flow-Erfahrung aus. Die Ergebnisse unterstützen die erwartete Verbesserung der Angst. Auch der wahrgenommene Stress nahm in der Versuchsgruppe ab – jedoch nicht in der Kontrollgruppe. Obwohl keine spezifischen Wirkungen auf eine der drei Aufmerksamkeitskomponenten des Aufmerksamkeitsnetzwerktests (dass heiβt Alarmierung, Orientierung und exekutive Aufmerksamkeit) gefunden wurden, verbesserten sich die Gesamtreaktionszeiten des Aufmerksamkeitsnetzwerktests in der Versuchsgruppe stark und hochsignifikant. Diese Verbesserung war in der Kontrollgruppe gleichermaßen nicht vorhanden. Auf der neuronalen Ebene wurden während der Orientierungs- und Exekutivsbedingungen des ANTs keine signifikanten interventions-assoziierten Aktivierungen beobachtet. Während des ANT-Alarmzustands ließ jedoch eine erhöhte interventions-assoziierte Gehirnaktivität im superioren frontalen Gyrus, im posterioren cingulären Kortex und im rechten Hippocampus in der Achtsamkeitsgruppe verzeichnen. Obwohl es keine Korrelation zwischen verringertem Stress und Aufmerksamkeitsleistung gab, fand sich eine signifikante Korrelation zwischen der verringertem Stress und Aktivität im rechten Hippocampus nach dem Achtsamkeitstraining. Die Werte der fraktionalen Anisotropie (FA) der weißen Substanz in der Versuchsgruppe verzeichneten einen signifikanten Anstieg im der rechten fasciulus uncinatus, indikativ für eine verstärkte Verbindungen zwischen dem rechten Hippocampus und frontalen Bereichen des Gehirns. CBF Ergebnisse einer ROI-Analyse (engl. region of interest) der grauen Substanz von Kernhirnregionen, für welche in früheren Studien Blutflussänderungen im Zusammenhang mit Achtsamkeitstraining berichtet wurden, zeigten eine signifikante Abnahme des CBF im Bereich des anterioren cingulären Kortex (ACC) als Konsequenz des Web-basierten Achtsamkeitsmeditationstraining; Korrelationen zwischen wahrgenommenem Stress und ACC-CBF-Werten zeigten eine weniger reaktive Reaktion auf Stress bei der Versuchsgruppe in dieser Gehirnregion im Vergleich zur Kontrollgruppe. Zusammenfassend legen die Ergebnisse dieser Studie nahe, dass ein kurzes online-basiertes Achtsamkeitstraining positive Auswirkungen auf die psychische Gesundheit (d.h. weniger Stress und Angst), auf die Aufmerksamkeitsleistung sowie die mentale Verfassung (d.h. erhöhte Flow-Erfahrung) haben kann, und sie legen einen Zusammenhang mit einer verbesserten Gehirnfunktion und allgemeinem Wohlbefinden nahe.

To my beloved parents,
Jayme *and* ***Lupita****.*

&

To the memory of my beloved uncle ***Dr. Aurelio Álvarez Zepeda****,*
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Abbreviations and Symbols

ACC	**a**nterior **c**ingulate **c**ortex
AC-PC	**a**nterior **c**ommisure - **p**osterior **c**ommisure
AD	**a**xial **d**iffusivity
ADHD	**a**tention-**d**eficit/**h**yperactivity **d**isorder
ANOVA	**AN**alysis **O**f **VA**riance
ANT	**a**ttention **n**etwork **t**ask
ASL	**a**rterial **s**pin **l**abeling
b	diffusion-weighting factor
BASIL	**B**ayesian **I**nference for **A**rterial **S**pin **L**abeling
BOLD	**b**lood-**o**xygen-**l**evel-**d**ependent
CBF	**c**erebral **b**lood **f**low
CBT	**c**ognitive **b**ehavioural **t**herapy
CC	**c**ingulate **c**ortex
CCC	**C**opyright **C**learence **C**enter
CONACYT	**C**onsejo **N**acional de **C**iencia **y** **T**ecnología
	(Mexican National Council of Science and Technology)
CSD	**c**onstrained **s**pherical **d**econvolution
d	Coehn's **d** effect size
DARTEL	**D**iffeomorphic **A**natomical **R**egis**t**ration using **E**xponentiated **L**ie algebra
df	**d**egrees of **f**reedom
dHb	**d**eoxy**h**emoglo**b**in
DLPFC	**d**orso**l**ateral **p**refrontal**c**ortex

DTI	**d**iffusion-**t**ensor-**i**maging
DWI	**d**iffusion-**w**eighted **i**maging
e.g.	**e**xempli **g**ratia (for example)
FA	**f**ractional **a**nisotropy
FD	**f**rame wise **d**isplacement
FEW-16	**F**ragebogen zur **E**rfassung des körperlichen **W**ohlbefindens
FLAIR	**fl**uid-**a**ttenuated **i**nversion **r**ecovery
fMRI	**f**unctional **M**agnetic **R**esonance **I**mage
FOV	**f**ield **o**f **v**iew
FSS	**F**low **S**hort **S**cale
FWE	**f**amily **w**ise **e**rror
FWHM	**F**ull **W**idth at **H**alf **M**aximum
EPI	**e**cho-**p**lanar-**i**maging
GE-EPI	**g**radient-**e**cho **e**cho-**p**lanar-**i**maging
GLM	**g**eneral **l**inear **m**odel
GM	**g**ray **m**atter
GRASE	**gr**adient- **a**nd **s**pin-**e**cho
HbO_2	**o**xy**h**emoglo**b**in
HRF	**h**aemodynamic **r**esponse **f**unction
IBMT	**i**ntegrative **b**ody-**m**ind **t**raining
i.e.	**i**d **e**st (that is)
IQR	**i**nter**q**uartile **r**ange
μ	mean
MAAS	**M**indfulness **A**ttention **A**wareness **S**cale
MB	**m**ulti**b**and
MBAT	**m**indfulness-**b**ased **a**rt **t**herapy
MB-BT	**m**indfulness-**b**ased **b**lood **p**ressure reduction
MBCT	**m**indfulness-**b**ased **c**ognitive **t**herapy
MBI	**m**indfulness-**b**ased **i**nterventions
MBSR	**m**indfulness-**b**ased **s**tress **r**eduction

MBP	**m**indfulness-**b**ased **p**rograms
MD	**m**ean **d**iffusivity
M.I.N.I	**M**ini-**I**nternational **N**europsychiatric **I**nterview
MNI	**M**ontreal **N**eurological **I**nstitute
MPRAGE	**m**agnetization **p**repared **r**apid **g**radient **e**cho
MR	**m**agnetic **r**esonance
MRI	**m**agnetic **r**esonance **i**maging
n	sample size
NA	**n**ot **a**pplicable
OCD	**o**bsessive- **c**ompulsive **d**isorder
p	**p** value
pCASL	**p**seudo-**C**ontinuous **A**rterial **S**pin **L**abeling
PCC	**p**osterior **c**ingulate **c**ortex
PFC	**p**re**f**rontal **c**ortex
PLD	**p**ost-**l**abeling **d**elay
PSS	**P**erceived **S**tress **S**cale
r	cor**r**elation coefficient
rmANOVA	**r**epeated-**m**easures **A**nalysis **O**f **VA**riance
rs-fMRI	**r**esting-**s**tate **f**unctional **M**agnetic **R**esonance **I**maging
ROI	**r**egion **o**f **i**nterest
RD	**r**adial **d**iffusivity
RT	**r**eaction **t**ime
σ	standard deviation
SLF	**s**uperior **l**ongitudinal **f**asciculus
SFG	**s**uperior **f**rontal **g**yrus
SMA	**s**ensori**m**otor **a**rea
SPM	**s**tatistical **p**arametric **m**apping
STAI	**S**tate and **T**rait **A**nxiety **I**nventory
SWCT	**S**troop **W**ord- **C**olor **T**ask
τ	labeling duration

T	**t**esla
TE	**e**cho **t**ime
TP	**t**ime **p**oint
TR	**r**epetition **t**ime
UNC	**unc**inate fasciculus
VBM	**v**oxel-**b**ased **m**orphometry
WM	**w**hite **m**atter
χ^2	**Chi**-squared test

Chapter 1

Introduction

1.1 Mindfulness Meditation

1.1.1 What is Mindfulness Meditation?

The roots of mindfulness meditation remote to the Buddhist traditions. More specifically, it is derived from a Buddhist meditation practice called *Vipassana* (Hart, 2020). The secularization of this practice gave rise to what we know today as mindfulness meditation, which mainly involves exercising of focused attention[1] and open monitoring[2] (Lutz et al., 2008). Mindfulnes meditation practice is a framework to achieve the mental state of mindfulness which is then defined as moment-to-moment (i.e., present-centered) awareness of thoughts, feelings, or sensations that are acknowledged and accepted free of judgement (Kabat-Zinn & Hanh, 2013).

Mindfulness practice has increasingly been adapted by clinical programs (Shonin et al., 2013), as well as in schools and companies, and research on the effects of such programs has exponentially increased over the past fifteen years (Baminiwatta &

[1] **Focused attention** consists in focusing the attention on something, e.g., in the breath.

[2] **Open monitoring** consists in focusing on whatever comes to our attentional field (i.e., awareness of thoughts or sensations) without judgement.

Solangaarachchi, 2021). Given the positive effects of such studies, mindfulness meditation has also been considered as a form of mental training that can enhance aspects of cognitive processing and cognitive capacities (Bishop et al., 2004).

1.1.2 Mindfulness Meditation Programs and Traditions

There are many mindfulness meditation programs and traditions, here I provide a brief overview of the most common ones:

- **Integrative body-mind training (IBMT)** refers to the practice of mindfulness meditation, Tai Chi, Yoga, and Qi Gong (Tang et al., 2017).
- **Iyengar Yoga**, named after his developer Bellur Krishnamachar Sundararaja (B.K.S) Iyengar, focuses on the practice of body/yoga postures (i.e., `asanas`) through the use of props such as belts, mats, pillows, etc. It also encourages the practice of breathing exercises and meditation (Iyengar, 2006).
- **Insight meditation** consists of practicing focused attention to internal experiences (Goldstein & Kornfield, 2001).
- **Mindfulness-based stress reduction (MBSR)** is an intensive eight-week mindfulness training program designed by John Kabat-Zinn focused to help people suffering from stress, anxiety, depression, and pain (Kabat-Zinn & Hanh, 2013).
- **Mindfulness-based art therapy (MBAT)** is an MBSR based program combined with art activities[3].
- **Mindfulness-based blood pressure reduction (MB-BT)** is also an MBSR based program adapted for individuals with hypertension and targeted to modify known determinants of blood pressure such as stress reactivity (Loucks et al., 2019).

[3]http://www.arttherapyandmindfulness.com/about/mindfulness-based-art-therapy/

- **Mindfulness-based cognitive therapy (MBCT)** combines mindfulness meditation practices with cognitive behavioural therapy (CBT) to help individuals cope with their thoughts; this in return reduces feelings of distress[4].
- **Mindfulness-based interventions (MBI)** or **Mindfulness-based programs (MBPs)** are any meditation program that incorporates mindfulness practices and theory to relief human distress by increasing joy, compassion, wisdom and improving attentional, emotional and behavioural self-regulation. Examples of this programs are MBAT, MB-BT, MBCT, and MBSR (Crane et al., 2017).
- **Templestay** is four-day intensive mindfulness meditation retreat program based on Korean Buddhism[5].
- **Tibetan Dzogchen** also known as Utmost Yoga is an Indo-Tibetan Buddhist tradition which aims to reach the `rigpa` (i.e., a state of pure awareness) through yoga postures, contemplation and meditation practices, breathing techniques, among others (Lama, 2006).
- **Zen** meditation is a Buddhist tradition that consists on the practice of open monitoring in a seated position (Dogen, 2004).

1.2 Effects of Mindfulness Practice on The Brain and Well-Being

1.2.1 Effects on Physical and Phsycological Well-Being

Numerous studies have been able to effectively demonstrate a positive effect of mindfulness training on individual's physical well-being (e.g., through stress reduction, improved cardiovascular health, better pain processing, and improved

[4]https://www.mbct.com
[5]https://eng.templestay.com/page-templestay.asp

immune function) in addition to improvements in mental health [e.g., through a decrease in depression, anxiety, drug dependence, attention deficit hyperactivity disorder (ADHD) symptoms, and eating disorders] (Chiesa et al., 2010; Davidson et al., 2003; Grossman et al., 2004; Hofmann et al., 2010; Khoury et al., 2015; Zeidan et al., 2011; Goldberg et al., 2018; Black & Slavich, 2016). Furthermore, recent mindfulness meditation findings have shown improvements in social behaviour (e.g., through an increased compassion, empathy, and improvements in communication skills), life satisfaction, creativity, and emotion regulation (Luberto et al., 2018; Kreplin et al., 2018; Amutio-Kareaga et al., 2017; Lamothe et al., 2016; Ostafin et al., 2015; Baas et al., 2014).

Of great interest is the stress and trait anxiety reduction that has been shown in multiple studies done with MBSR trainings (Chiesa & Serretti, 2009; Kabat-Zinn & Hanh, 2013; Goyal et al., 2014; Khoury et al., 2015; Crowley et al., 2022; Basso et al., 2019), as it has been documented that prolonged periods of stress and trait anxiety have detrimental effects on cognitive performance, specifically on attentional control, working memory, response inhibition, among others (Girotti et al., 2018; Jiang & Rau, 2017; Luethi et al., 2009; Du et al., 2022). It is therefore possible, that some of the positive effects of mindfulness practice on cognitive functioning (see section 1.2.2) are related to or a consequence of stress and trait anxiety reduction. However, the association between improvement of cognitive functions, decreased stress levels, and trait anxiety as a result of a mindfulness training is still a matter of research.

1.2.2 Effects on Cognition

Many studies have been able to demonstrate improvements in various aspects of cognitive processing in mindfulness meditation practitioners such as executive attention[6], working memory, and problem-solving skills (Bishop et al., 2004; Chiesa

[6]**Executive attention** is the mechanism that blocks distracting information when trying to achieve a goal.

et al., 2011; Jha et al., 2007). However, findings in this field of research are a bit less univocal (Im et al., 2021; Lao et al., 2016; Whitfield et al., 2021) and more research is needed. A recent meta-analysis investigating the neurobiological effects of mindfulness meditation interventions on cognition did not observe significant effects on attention (i.e., sustained[7] and selective[8]), working memory, and long-term memory; however, they indicated a small effect on executive attention (Im et al., 2021). In the following section, a detailed overview of previous findings of mindfulness studies in attention and their underlying brain regions is given.

1.2.2.1 Effects on Attention and Underlying Brain Regions

The preferred method used by neuroscientists to investigate the effects of mindfulness meditation on attention and its underlying brain regions is functional magnetic resonance imaging (fMRI), based on blood-oxygen-level-dependent (BOLD) contrast. BOLD contrast also known as BOLD signal surges from the different magnetic properties of oxygenated (i.e., diamagnetic) and deoxygenated (i.e., paramagnetic) hemoglobin. During neural activity, following the principle of neurovascular coupling, there is an increase in cerebral blood flow (CBF) relative to the oxygen cosumption [i.e., increased in amount of oxyhemoglobin (HbO_2) relative to the amount of deoxyhemoglobin (dHb)]; this change in ratio, and therefore, in the magnetic resonance (MR) signal, changes the contrast in the magnetic resonance image, which in turn is interpreted as an indirect measurement of brain activity (see Figure 1.1) (Ogawa et al., 1992).

Neuroscience studies have revealed that several brain regions implicated in attentional processes such as the cingulate cortex (CC) and prefrontal cortex (PFC) are being altered through mindfulness practice (Sperduti et al., 2012; Zsadanyi et al., 2021). Figure 1.2 shows a depiction of these brain areas. The anterior cingulate

[7]**Sustained attention** is the ability to focus on a task or stimulus over an extended period of time.

[8]**Selective attention** is the ability to focus on a particular task or stimulus among different ones.

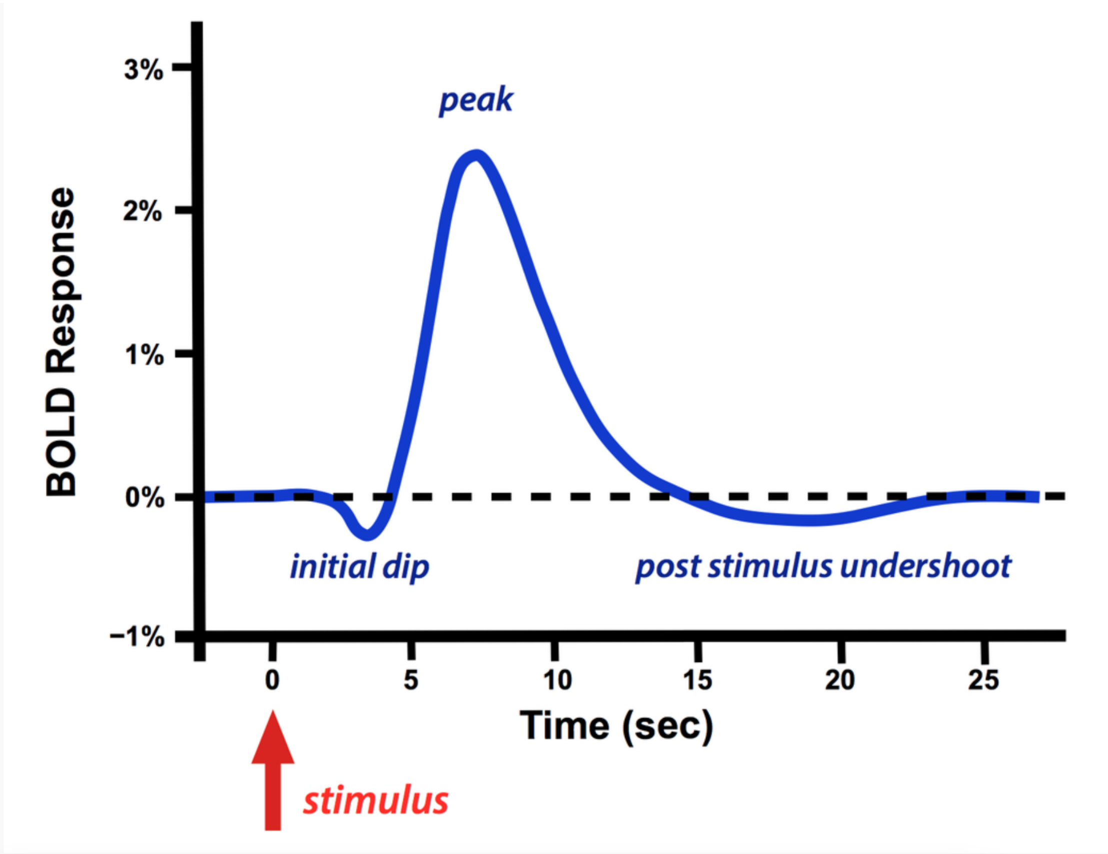

Figure 1.1: BOLD Haemodynamic Response Function (HRF). This figure shows the BOLD HRF following a single brief stimulus. The x-axis depicts the time after the stimulus, and the y-axis the percentage change of the MRI signal. Image courtesy of Allen D Elster, MRIQuestions.com

cortex (ACC) is a region that is known to play a prominent role in executive processing and, more specifically, in executive attention (van Veen & Carter, 2002). In fact, several fMRI studies have demonstrated an increase in ACC activation in experienced meditators (Fox et al., 2016; Hölzel et al., 2007), while linking this increase in ACC activation to a direct consequence of a mindfulness training (Tang & Posner, 2009). Interestingly, improvements in executive attention have also been observed in studies following short mindfulness training interventions; these shorter training sessions were comprised of 20-min sessions per day for three to five days (Tang et al., 2007; Wenk-Sormaz, 2005). A follow up study evaluating the effects of a short mindfulness training [30-mins of IBMT for five days] in naïve subjects found enhanced CBF in subgenual/adjacent ventral ACC (Tang et al.,

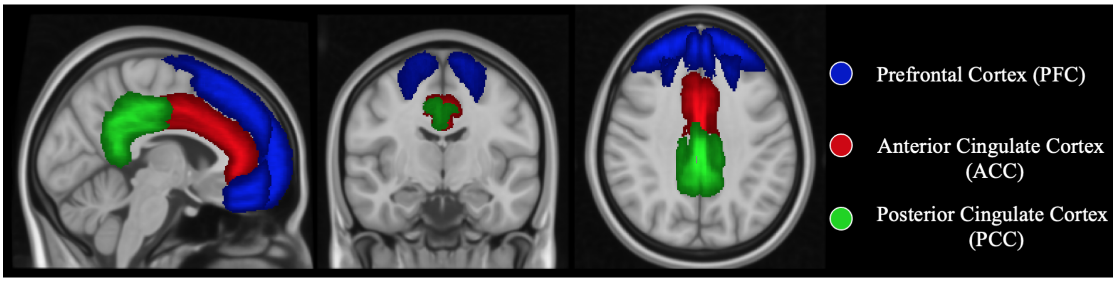

Figure 1.2: Depiction of Prefrontal Cortex (PFC), Anterior Cingulate Cortex (ACC), and Posterior Cingulate Cortex (PCC). This figure was made with FSLeyes using the Harvard-Oxford Atlas.

2015). And, a recent mindfulness study was even able to detect a direct association between the improvement in executive attention and increased activation in both the right ACC and the right dorsolateral prefrontal cortex (DLPFC) using the Attentional Network Task (ANT) (Kwak et al., 2019).

In addition to the changes observed in ACC activations, several resting state studies found that mindfulness training had an effect on posterior areas of the cingulate cortex while also reporting an increase in functional connectivity between the posterior cingulate cortex (PCC), dorsal ACC, and DLPFC (Brewer et al., 2011; Creswell et al., 2016; Kral et al., 2019). Another study looking at structural changes following MBSR programs even found an increased gray matter (GM) concentration in the PCC indicating that the PCC is a region which is very susceptible to the effects of mindfulness meditation (Hölzel et al., 2011).

Furthermore, studies investigating the effects of mindfulness trainings on the PFC have also shown changes in the BOLD signal in this area after the intervention. For example, Tomasino & Fabbro (2016) found increased activation in the right DLPFC and decreased activation in the rostral PFC on naïve-meditators after an eight-week focused attention based mindfulness meditation, and Ives-Deliperi et al. (2013) found increased medial PFC activations after a mindfulness based cognitive therapy in patients with bipolar disorder. Moreover, a study investigating CBF differences between experienced meditators and non-meditators found a significant higher CBF in the PFC of long-term meditators (Newberg et al., 2010).

The PFC is an essential brain structure for executive functions[9], and lesions in the DLPFC have shown alteration in working memory, rule learning, planning, attention, and motivation (Szczepanski & Knight, 2014). Therefore, investigating PFC changes after a standardized short-mindfulness training is within our interest. However, it can be assumed that there are several other brain regions involved in the enhancement of attention through mindfulness meditation.

1.2.3 Effects on White-Matter Tracts

Diffusion-tensor-imaging (DTI) is a magnetic resonance imaging (MRI) technique that allows us to image the white matter (WM) tracts of the brain thanks to the brownian motion (i.e., random motion) of water molecules. This motion, also known as diffusion, can be isotropic or anisotropic. Isotropic diffusion refers to the motion of water molecules not being restricted or restricted in all directions. On the other hand, anisotropic diffusion is when the movement of water molecules is hindered by the microstructure of the tissue in neural fibres; therefore, by measuring this anisotropy, indirect information about the microstructural integrity of white matter tracts is provided (Beaulieu, 2002). Fractional anisotropy (FA) is a value between cero and one that describes the degree of anisotropical diffusion (i.e., cero means isotropic diffusion and one represents restricted diffusion in all but one direction). Other important measurements that describe axonal properties in white matter are the mean, axial, and radial diffusivity. Mean diffusivity (MD) gives a measurement of the total diffusion (i.e., total movement of water molecules) within a voxel or region of interest (ROI). Axial diffusivity (AD) describes water diffusion parallel to the axonal fibers, while radial diffusivity (RD) refers to water diffusion perpendicular to the axonal fibers.

Cross-sectional DTI studies of long-term meditators compared to non-meditators have shown increased FA values in major white matter projection pathways (i.e.,

[9]Examples of **executive functions** are executive attention, cognitive inhibition, working memory, planning, and flexible thinking.

corticospinal tract and corona radiata), association pathways [i.e., cingulum, superior longitudinal fasciculus (SLF), and uncinate fasciculus (UNC)], and commissural pathways (i.e., corpus callosum and anterior commissure) (Nakata et al., 2014; Tang et al., 2015; Zsadanyi et al., 2021). Figure 1.3 shows a depiction of the previously mentioned WM tracts. Longitudinal DTI studies done on naïve meditators following a short-term mindfulness training have confirmed some of these findings as a result of a mindfulness training. For example, Tang et al. (2010) showed that 11 h of IBMT spaced in four weeks increased the FA in the corona radiata of 22 young healthy undergrads compared to an active control group matched for age and sex that received a relaxation training. The corona radiata is a major WM projection tract connecting the ACC with other brain structures. A follow up study of the same group with the same experimental settings showed that five hours of IBMT spaced in two weeks were not able to increase the FA nor the RD in areas surrounding the ACC, but reductions in the AD were detected (Tang et al., 2012). A recent study looking at plastic changes in WM after a Templestay program found increased FA in the left SLF, left posterior corona radiata, and splenium of the corpus callosum, which are regions known to be important for cognitive functions (Yoon et al., 2019). And, an MBSR study by Kral et al. (2019) on meditation-naïve participants with an active and waitlist control group found a larger resting state functional connectivity between the PCC and the DLPFC in the mindfulness group that was associated with an increased microstructural connectivity in the SLF, which is the white matter tract connecting the PCC and the DLPFC. In this study, white matter microstructure was assessed through several DTI measurements (i.e., FA, MD, RD, and AD).

DTI studies investigating the effects of mindfulness meditation have successfully demonstrated the appearance of neuroplastic changes in improved brain function; for this reason, I included DTI measurements in our research as to have more resources that would help us better understand improvements in attention and pyschological outcomes as consequence of mindfulness training.

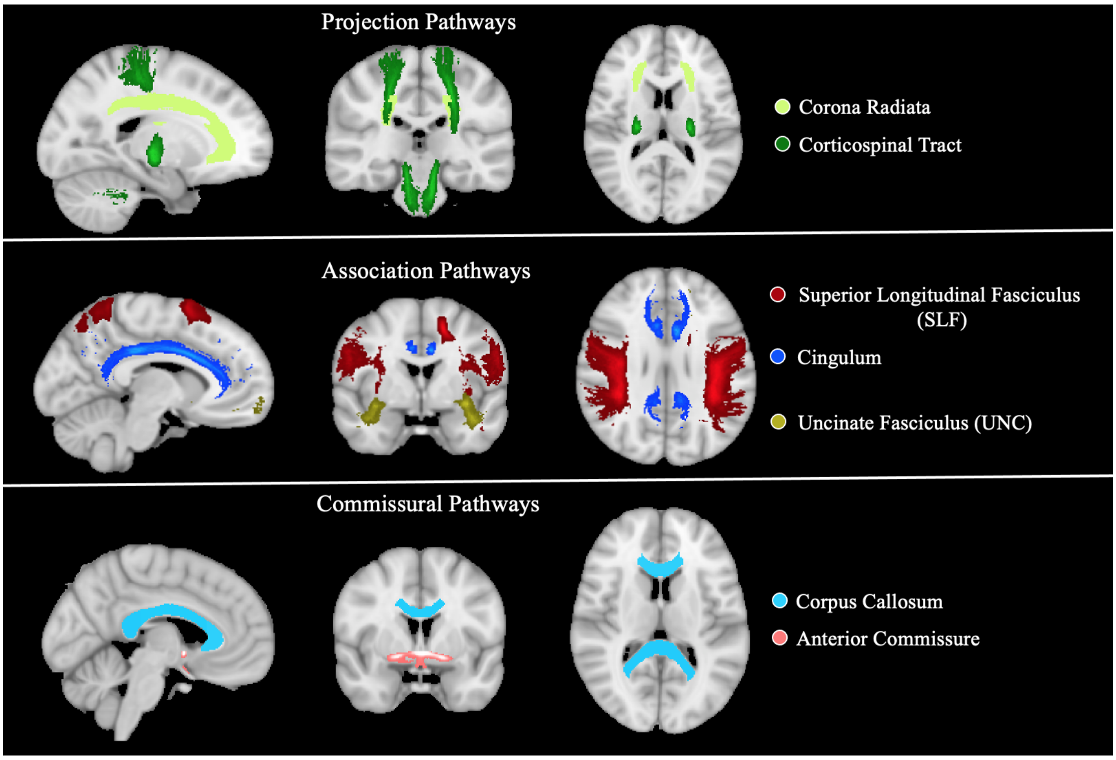

Figure 1.3: White Matter Pathways Susceptible to Meditation. This figure shows a depiction of projection, association and commissural pathways susceptible to mindfulness trainings/programs. This figure was made with FSLeyes using the JHU ICBM-DTI-81 White-Matter, JHU White-Matter Tractography, and XTRACT HCP Probabilistic Tract Atlases.

1.2.4 Effects on Cerebral Perfusion or CBF

Nutrients and oxygen are transfered from the blood to brain tissue through the capillary beds in a process called cerebral perfusion also known as cerebral blood flow. CBF is defined as the quantity of blood in ml delivered per 100 g of tissue in one minute. Typical CBF values in GM of the human brain are between 40 and 100 ml/100g/min (Alsop et al., 2015). Thanks to CBF measurements we have indirect access to brain metabolism (i.e., brain function) as there is a high coupling between oxygen delivery and consumption (Barker et al., 2013). Unfortunately, studies on CBF are not very popular as the vast majority of the methods to measure CBF need the use of an external contrast agent, which implies an increased risk of nephrogenic systemic fibrosis and allergic reactions in the study population;

it is therefore not suitable for everyone specially for children, and contraindicated in patients with renal failure. Other disadvantages of perfusion methods with contrast agents are their long set-up times, difficulty to apply them on longitudinal studies, and the increased in cost. However, a relative new and accesible MR method named arterial spin labeling (ASL), which uses water molecules as en endogenous tracer for imaging cerebral perfusion, is expanding the use of CBF measurements in neuroscience studies (Koretsky, 2012).

Differences in cerebral blood flow patterns have been seen between long-term meditators and non-meditators. Specifically, long-term meditators have shown an asymmetry in their thalamic activity and increased CBF in the prefrontal cortex (as described in section 1.2.2.1), parietal cortex, putamen, caudate, and midbrain (Newberg et al., 2010) (see Figure 1.4 for a depiction of these brain areas). However, it is yet not clear if this difference in CBF values is the result of mindfulness training or if brains of meditators are per se different from brains of people that do not pursue meditation as a practice. A preliminary evaluation of CBF effects of a 12-week Iyengar Yoga training program in four naïve subjects showed reduced CBF values in the right amygdala, right dorsal medial cortex, and right sensorimotor area (SMA) (Cohen et al., 2009). And as reported in section 1.2.2.1, a most recent study using a short mindfulness training (30-mins of IBMT for five days) in 20 naïve subjects found enhanced CBF not only in subgenual/adjacent ventral ACC, but also in the medial prefrontal cortex and insula, not seen in their active control group [sample size (n) = 20] that underwent a relaxation training (Tang et al., 2015). Another study done on women with breast cancer that followed an MBAT program found significant CBF increases in the left caudate at resting state that significantly correllated with deceased scores in anxiety; this was not present in their control group (Monti et al., 2012). Figure 1.4 illustrates brain areas of naïve meditators that have shown changes in CBF. While these studies have given some direction on the effects of mindfulness meditation in CBF, there is still a need for more neuroscience studies looking not only at reproducibility, but also at psychological and physiological correlations that will help in interpretation

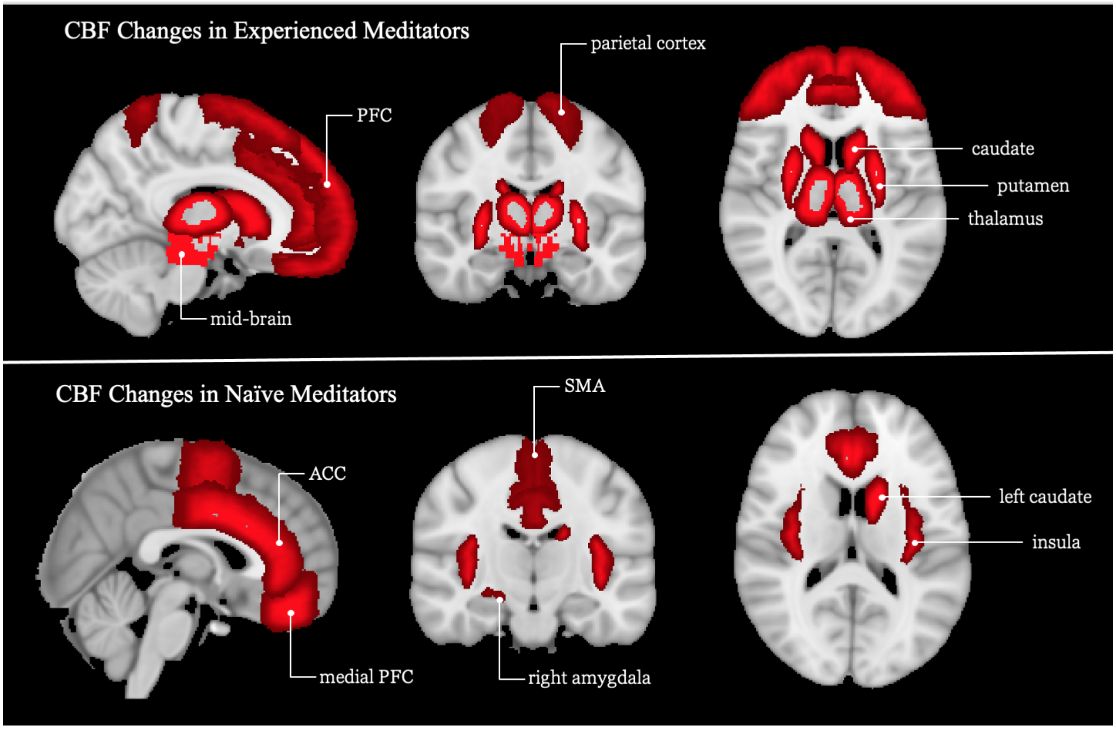

Figure 1.4: Brain Areas Susceptible to CBF Changes in Mindfulness Meditators. This figure depicts brain areas susceptible to CBF changes in experienced and naïve mindfulness meditators. This figure was made with FSLeyes using the Talarach Daemon and Harvard-Oxford Cortical/Subcortical Atlases.

of these CBF changes seen on meditators. For this reason, CBF measurements acquired with ASL were also included in the study presented in this thesis.

Chapter 2

Aims and Hypotheses

2.1 Event-Related fMRI and Psychological Outcomes Analyses

2.1.1 Aims

Given the recent advances made in the field of neuroimaging, the neurobiological effects of an intervention training on functional brain activation can now more accurately be investigated. While previous studies reported the impact of mindfulness training on attention and executive functions, as well as the relevance of these processes in everyday life, the present study sought to investigate the neural and behavioural training effects on the three main components of attention (i.e., alerting, orienting, and executive attention) in more detail and its association with changes in stress and anxiety using robust and updated analyses procedures. While most published studies to date still suffer from poor methodological quality, I implemented state-of-the-art methods including an active control group, randomization, and pre- and post-intervention measurements (i.e., longitudinal study). In addition, I investigated the effects of the training on other relevant psychological outcome parameters such as mindfulness and flow experience, and their correlation with brain activation in order to explore possible mechanisms of action behind the cognitive training effects.

2.1.2 Hypothesis

I expected to observe an improvement in attention (i.e., faster reaction times in the ANT) together with elevated activation patterns in the CC and PFC, going along with reductions in stress and anxiety. It was also hypothesized that mindfulness training would increase perceived mindfulness, physical well-being, and flow experience.

2.2 White Matter Tracts Analysis Using DTI

2.2.1 Aims

The aim was to investigate if a 31-day web-based mindfulness training can alter white matter FA values (i.e., increased connectivity) between brain areas that showed a significant interaction between the experimental and control group among timepoints in the event-related ANT fMRI study.

2.2.2 Hypothesis

An increased FA in main white matter tracts connecting brain regions that showed a significant interaction between the experimental and control group among timepoints in the event-related ANT fMRI study.

2.3 Perfusion Analysis Using ASL

2.3.1 Aims

The present study investigated the CBF effects of a 31-day web-based mindfulness meditation training on gray matter of core brain regions known to be involved in mindfulness meditation and perfusion changes (i.e., frontal lobe, superior parietal lobule, ACC, thalamus, putamen, caudate, and right amygdala).

2.3.2 Hypothesis

I hypothesized that the mindfulness meditation training would go along with a greater asymmetry in the thalamic activity, and an altered CBF in the frontal pole, superior parietal lobule, insula, ACC, putamen, caudate, and right amygdala.

Chapter 3

Materials and Methods

3.1 Subjects

Participants were recruited via flyer distributions, online advertisements, and word-of mouth based on their interest in participating in a health-enhancement program. Our inclusion criteria were as follows:

- All participants were screened using the Mini-International Neuropsychiatric Interview (M.I.N.I) (Sheehan et al., 1998) and had no previous or current diagnosed psychiatric or neurological diseases,
- participants reported taking no psychotropic drugs,
- participants needed to be naïve meditators (i.e., participants could not have practiced more than three meditation sessions in the last year or more than ten meditation sessions over the course of their life),
- age range between 15 and 65 years old,
- German proficiency, and
- right-handedness.

Before the main study, I performed a pilot study to test the adequacy of the task investigating the effects of the mindfulness training on the different cognitive processes (i.e., attention conditions) assessed by the ANT. Figure 3.1 shows the demographics and descriptive statistics of the participants included in the final pilot, behavioural (i.e., pyschological outcomes), and fMRI study. A monetary compensation was given to the subjects for their participation, and access to both courses was given to each participant after their intervention.

3.2 Procedure

Written informed consent was obtained from all participants, and the ethics committee from Klinikum rechts der Isar, Technical University of Munich approved this study. Subjects were screened/scanned no more than two weeks prior to their first training session. All subjects were scanned in a 3T Philips Ingenia MR-Scanner (Philips Healthcare, Best, The Netherlands) at Klinikum rechts der Isar. Participants completed standardized questionnaires prior to, and upon completing the training, which assessed their physical well-being [Fragebogen zur Erfassung des körperlichen Wohlbefindens, FEW-16 (Kolip & Schmidt, 1999)], stress levels [Perceived Stress Scale, PSS (Cohen et al., 1983)], perceived mindfulness [Mindful Attention Awareness Scale –German version, MAAS (Brown & Ryan, 2003; Michalak et al., 2008)], anxiety [State and Trait Anxiety Inventory, STAI (Spielberger et al., 1999)], and flow experience [Flow Short Scale, FSS (Stiensmeier-Pelster & Rheinberg, 2002)]. Following the pre-training assessment and scanning, participants were randomized to either the mindfulness or health-enhancement program. This study was a single blinded study as all subjects were only informed that they were participating in a training to improve their overall health, i.e., no meditation training was mentioned prior to the start of the intervention/training. After the intervention, participants were directly asked how many training sessions did they complete. Enrollment in the respective trainings was checked through the course

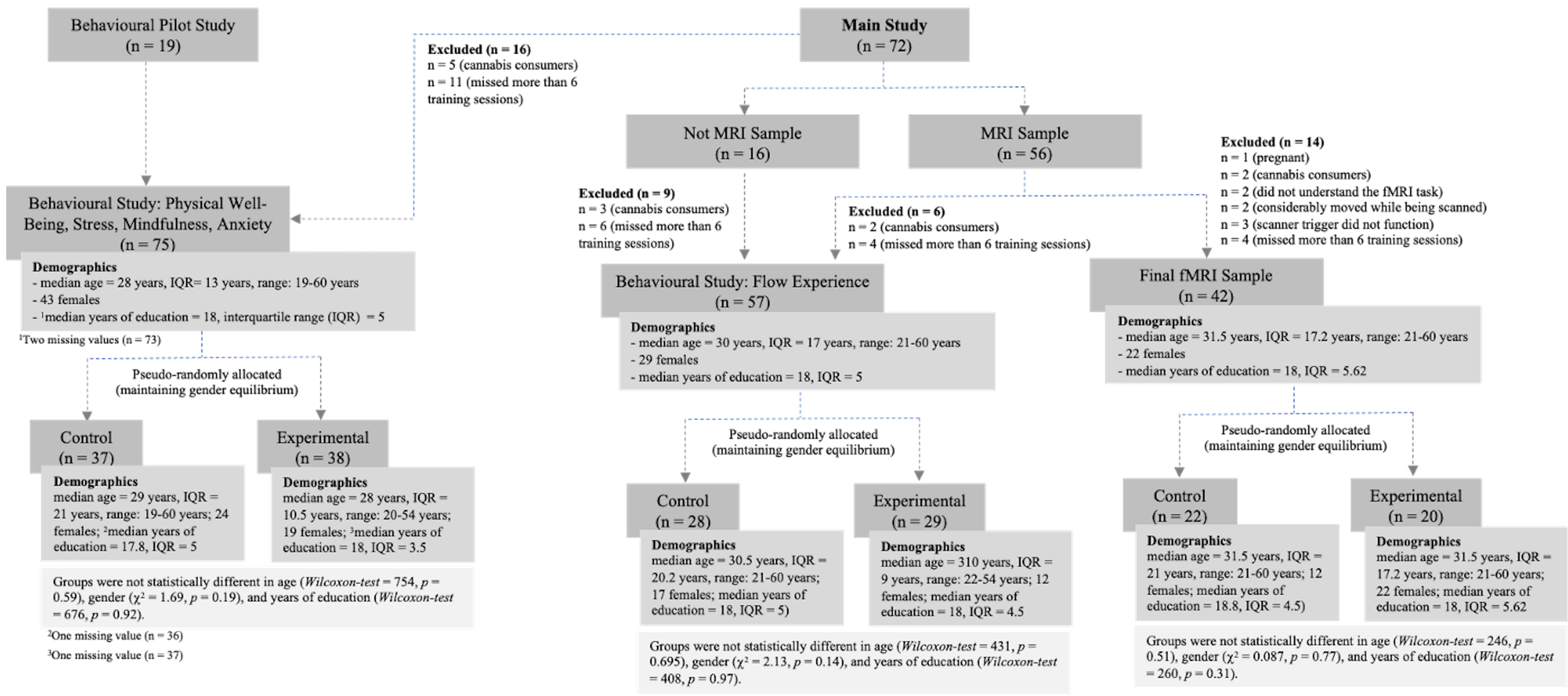

Figure 3.1: Demographics and Descriptive Statistics of Study Participants

online platform: Teachable[1]. All participants in both the experimental and the control group had to complete at least 25 sessions to be included in the study. Participants then underwent the identical testing and scanning procedure within two weeks following the end of their program/training.

3.3 Training

Both training courses were structured in a similar manner in which every three days a 15-minute video was shown, which was followed by two days of 15-minute podcasts or audio recordings. This pattern repeated for the duration of the 31-day course. Videos and audios were framed by short texts to highlight the take-aways of the topic of that day. A detailed overview on both trainings can be found in Appendix A.

3.3.1 Mindfulness Meditation Training

The mindfulness course[2] was based on the MBSR program and developed in close cooperation with Dr. Britta Hölzel (BKH), a highly experienced MBSR instructor and mindfulness researcher, and contained guided meditation exercises and various mindfulness exercises, in addition to theoretical concepts and explanations provided in German by BKH. More specifically, theoretical topics included mindfulness research, mind wandering, body awareness, stress physiology, dealing mindfully with pain and difficult emotions, loving kindness, self-perception, connectedness, among others. Audio-guided meditations instructed participants to focus on various objects of attention, such as the breath, body sensations, emotions, thoughts, and sensations of walking, and to encounter experiences non-judgmentally, with acceptance and kindness. Loving kindness and open monitoring practice were included.

[1] https://teachable.com
[2] https://iam-onlinetraining.de

3.3.2 Health-Enhancement Program

The course on 'everyday health' was developed specifically as an active control training that resembled the mindfulness meditation training in all aspects but did not contain any information or active training in mindfulness or meditation in general. This course provided participants with information on health-related topics such as sleep, burn-out, aging, and nutrition.

3.4 Acquisition of MRI data

All MR imaging was performed on a 3T Philips Scanner, equipped with a 32-channel head coil at Klinikum Rechts der Isar in Munich, Germany. Our imaging protocol consisted on the following sequences:

1. T1-weighted MPRAGE –magnetization prepared rapid gradient echo–,
2. FLAIR –fluid-attenuated inversion recovery–(acquired for clinical purposes),
3. DTI,
4. event-related fMRI using an adapted event-related ANT of Fan et al. (2005),
5. resting-state fMRI (rs-fMRI),
6. T2*- weighted images (field-map), and
7. 3D GRASE –gradient- and spin-echo– pseudo-continuous ASL (pCASL).

Structural scans, with 230 anterior commisure-posterior commisure (AC-PC) axial slices (0.7 mm interslice gap) were acquired using the T1-weighted MPRAGE sequence with echo time (TE) = 5.2 ms, repetition time (TR) = 11 ms, flip angle = $8°$, field of view (FOV) = $256 \times 240 \times 161$ mm^3, and an isotropic voxel high-resolution of $0.7 \times 0.7 \times 0.7$ mm^3. For DTI, diffusion-weighted images (DWI) were acquired with a TR = 5643 ms, TE = 96 ms, FOV = $224 \times 256 \times 132$ mm^3, and an isotropic voxel resolution of 2 mm. Diffusion-sensitizing gradient echo encoding was applied in 64 directions using a diffusion-weighting factor (b) of 1400 s/mm^2. The total DWI acquisition time was 8 min. Whole brain functional scans, with 63 AC-PC axial slices (0.2 mm interslice gap) were acquired using a T2*-weighted 2D single shot gradient echo planar (GE-EPI) sequence, multiband (MB) Factor = 3, TE = 33 ms, TR = 1550 ms, flip angle = 70°, FOV = $192 \times 192 \times 138.4$ mm^3, and an 8 mm^3 isotropic voxel resolution. To estimate the corresponding field maps to correct for EPI-distortions (Jezzard & Balaban, 1995), two simple T2*-weighted images were acquired using a gradient echo sequence with two different TEs (long TE = 10.54 ms, short TE = 6.0 ms). FOV, spatial resolution, and number of slices were the same as for the functional scans. The 3D pCASL imaging parameters were as follows: FOV = $240 \times 240 \times 6$ mm^3, voxel resolution = $3 \times 3 \times 6$ mm^3, TR = 4.2 s, TE = 11 ms, PLD = 1.8 s, labeling duration (τ) = 1.8 s, and 8 averages. The total scan time was ∼45 min. Participants were asked to keep their eyes closed during rs-fMRI and pCASL acquisitions to avoid BOLD signal and CBF changes in the occipital regions.

3.5 Envent-Related Functional MRI

3.5.1 Attentional Network Task

The ANT is a paradigm designed to measure the efficiency of the alerting, orienting, and executive control networks of attention (Fan et al., 2002). An adapted version of this task can be also used to detect the brain activity of these attentional networks (Fan et al., 2005). Figure 3.2 shows a depiction of the ANT task used in this study. The stimuli of the MRI task consisted of three cue conditions (no cue, center cue, spatial cue) and two target conditions (congruent target, and incongruent target). The no cue condition presented a fixation cross in the center of the image and was the baseline condition of this paradigm. The center cue condition consisted of a fixation cross with an asterisk overlaid in the center of the screen, and its function was to alert participants to the onset of the upcoming target. The spatial cue condition was an asterisk displayed on the side of the screen where the target condition was going to be presented, thus orienting the attention of the participants towards the upcoming target. The duration of each cue was 200 ms. In the target condition a column of five horizontal arrows pointing leftward or rightward were shown. The task was to recognize the direction of the center arrow. In the congruent condition all arrows were pointing to the same direction, whereas in the incongruent condition the center arrow was pointing in a different direction, thus introducing a response conflict. The participants had to press a button with the index finger of their right hand to indicate if the center arrow was pointing to the left, and press a button with the middle finger of their right hand if the center arrow was pointing to the right. There were two runs in this experiment which each consisted of 36 trials. Conditions were counterbalanced and randomly generated. The experimental paradigm was programmed and presented to the participant using the Presentation® software (Version 20.1, Neurobehavioral Systems, Inc., Berkeley, CA, United States)[3].

3.5.2 Analysis of fMRI Data

Preprocessing and the event-related analysis of the functional images were conducted using statistical parametric mapping (SPM12, The Wellcome Centre for Human Neuroimaging, London, UK). Participants with a frame wise displacement ($FD_{mean} > 0.25$) were excluded (Power et al., 2012; Siegel et al., 2014). Our pipeline to preprocess the data was as follows: Realignment to the mean functional imaging and unwarping of fMRI time-series, co-registration of anatomical MRI to mean functional image, segmentation of anatomical images, creation of a group specific diffeomorphic anatomical registration using exponentiated lie

[3] https://www.neurobs.com

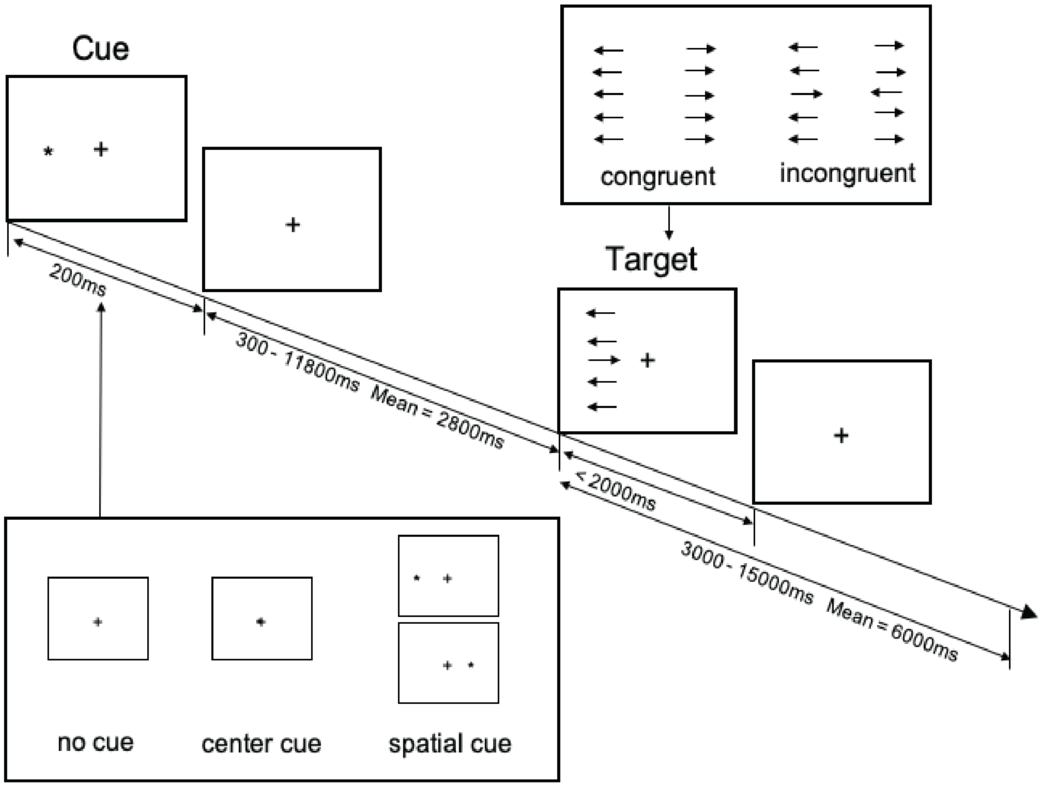

Figure 3.2: A Simplified Version of the ANT. Arrows were presented in a column on the right or left side of the screen, instead of in a row on the upper or lower part of the screen as seen in the original ANT arrangement. In-house pilot behavioural experiments showed a greater effect in the orienting network of attention with this vertical arrangement. Figure adapted from Fan et al. (2005). Licence Number: 5271351122300 given by Elsevier and the Copyright Clearance Center (CCC) to reuse and adapt this figure for this thesis.

algebra (DARTEL) template for normalization purposes (Ashburner, 2007), normalization to Montreal Neurological Institute (MNI) space, and smoothing with a 4 mm full width at half maximum (FWHM) Gaussian Kernel. Slice time correction was not performed as a multiband sequence was used to acquire the data and the TR used was less than 2 s, which should make the acquisition robust enough to avoid slice timing problems (Poldrack et al., 2011).

Based on the General Linear Model (GLM), a canonical HRF was convolved on the onsets of the events within the time series to create a statistical model of the ANT for each subject. Design matrices of the first level analysis consisted of five events (regressors): no cue (i.e., fixation cross), center cue, spatial cue, congruent target, and incongruent target. Six additional movement regressors were also added to the design matrix as nuisance regressors. To test the ANT paradigm, a one sample t-test including all participants was run on the fMRI data to see the activation of the three different ANT attentional networks. The second level analysis of the control and experimental data was performed using a two-way repeated measurements factorial analysis of variance (ANOVA) on the contrasts of interest: alerting (center cue – no cue), orienting (spatial cue – center cue), and executive attention (incongruent target – congruent target). The height (intensity) threshold was set at an uncorrected p = 0.05. Multiple comparison correction at $p < 0.05$ was determined by a Monte Carlo simulation yielding a cluster size threshold of 350 voxels ($2 \times 2 \times 2$ mm^3). The parameters of the simulation were the following: SPM volume in voxels (x = 64, y = 77, z = 50), local p = 0.05, one tail, global p = 0.05, fwhm = 2 voxels, number of iterations = 1500, t-distributed, df = 80, number of maps = 3)[4]. Parameter estimates of the activated clusters were obtained using MarsBaR (Brett et al., 2002). 2D visualizations of attentional networks wered created with SPM and WFU_PickAtlas (Tzourio-Mazoyer et al., 2002; Maldjian et al., 2003, 2004; Lancaster, 1997; Lancaster et al., 2000). 3D visualizations of fMRI images with a significant interaction were created following Madan (2015) Guide.

3.6 Behavioural Analysis

Training effects on the attentional networks were assessed by three-way mixed ANOVAs with time (pre and post) and network conditions (i.e., no cue and centered cue as the alerting network conditions, centered cue and spatial cue as the orienting network conditions, and congruent and incongruent target as the executive network conditions) as within-subject factors, and group (control and experimental) as a between-subject factor on the reaction times of the ANT task as

[4] `https://github.com/mbrown/fmrimontecluster/blob/master/fMRIMonteCluster.m` by Grown, M. R. G. 2013

seen in Kwak et al. (2019). Effects on stress levels, mindfulness, anxiety, physical well-being, and flow experience were assessed by two-way mixed ANOVAs (with time as the within-subject factor, and group as the between-subject factor). Data distributions of the behavioural questionnaires are visualized in raincloud plots (Allen et al., 2019). Effect sizes were calculated using Cohen's d (see Equation 3.1). Outliers were removed. Statistical analyses were conducted using R (The R Foundation for Statistical Computing, Vienna, Austria)[5].

$$Cohens'd = \frac{\mu}{\sigma^2\sqrt{1-r}},\ where\ \mu = \overline{RT_{TP1} - RT_{TP2}} \tag{3.1}$$

$$\sigma = \text{standard deviation},\ r = \text{correlation coefficient},$$
$$RT = \text{Reaction Time},\ TP = \text{Time Point}$$

3.7 Preprocessing and Analysis of DTI Data

The DTI data was first denoised with MRtrix3 (Tournier et al., 2019) and the rest of the preprocessing was done with Explore DTI (Leemans et al., 2009)[6]. The preprocessing pipeline was as follows: Denoising algorithm from MRtrx3 (*dwidenoise*), signal drift correction, Gibbs ringing correction, Venetian Blinds correction, motion and EPI/eddy current distortion corrections. The preprocessed images were fitted to the tensor model at each voxel, and FA maps were calculated. The automated/atlas based ROI analysis from Explore DTI was used to extract the FA values of important white matter tracts connecting our ROIs (i.e., PCC, PFC, and right hippocampus). The WM tracts of interest were the SLF (connecting the PCC to the PFC), and the right UNC (connecting the right hippocampus to the PFC). The atlas used was the "JHU ICBM-DTI-81 White-Matter Labeles" atlas (Mori et al., 2005). To find the interaction effects, two-way repeated-measures ANOVA (rmANOVA) (group as between-subjects factor and

[5] https://www.r-project.org
[6] http://exploredti.com

time as within-subjects factor) was conducted on the FA values of the SLF and the right UNC. The statistical tool used for this analysis was JASP version 0.16 (The Jasp Team, Amsterdam, The Neterlands) (JASP Team, 2022). Multiple comparisons were corrected using the Bonferroni method (Bonferroni, 1936). Statistically significant changes in FA where visualized using raincloud plots (Allen et al., 2019). For illustration purposes, fiber tractography was done following the constrained spherical deconvolution (CSD) model (Jeurissen et al., 2011; Tax et al., 2014).

3.8 CBF Quantification and ROI Analysis

CBF was quantified, corrected for partial volume effects and motion using BASIL: Bayesian Inference for Arterial Spin Labeling[7] (Chappell et al., 2011, 2009; Groves et al., 2009) on the pCASL data. The quality check of the CBF maps was based on good gray matter depiction of CBF, and that CBF values in gray mater were ∼2 times higher than the CBF values in white matter. ROI parcellation was based on the Harvard-Oxford atlas (Makris et al., 2006; Frazier et al., 2005; Desikan et al., 2006; Goldstein et al., 2007). To detect significant interactions a two-way rmANOVA (group as between-subjects factor and time as within-subjects factor) analysis was performed with the absolute CBF values of the brain regions of interest. Outliers were removed and multiple comparisons were corrected using the Bonferroni method (Bonferroni, 1936). Statistical analyses were conducted in R and visualized in raincloud plots (Allen et al., 2019).

[7] `https://asl-docs.readthedocs.io/en/latest/index.html`

3.9 Correlation Analyses

3.9.1 Correlation Analysis Between Brain Activations, ANT RTs, and Psychological Outcomes

Based on my hypothesis and on positive statistically significant results of the psychological outcomes (i.e., reduced stress and trait anxiety, and increased flow experience after the mindfulness intervention), assessment of Pearson's correlation was performed between:

- PSS and ANT-Reaction times,
- trait anxiety and ANT-Reaction times,
- flow experience and ANT-Reaction times,
- PSS and brain activations,
- ANT Alerting Effect (center cue RT – no cue RT) and brain activations,
- ANT Alerting Cue (center cue RT) and brain activations,
- trait anxiety and brain activations, and
- flow experience and brain activations

Pearson's correlations were corrected for multiple comparisons using the Holm's method (Holm, 1979). Python programming language (Python Software Foundation)[8] was used to perform correlation analysis and illustrations.

[8] https://www.python.org/

3.9.2 Correlation Analysis Between FA Changes, ANT RTs, and Psychological Outcomes

Pearson's correlations between FA changes in white matter tracts where the two-way rmANOVA detected a significant interaction (i.e, the right UNC) and changes in stress perception, trait anxiety, flow experience, and ANT RT were assessed. Python programming language was used to perform correlation analysis.

3.9.3 Correlation Analysis Between CBF Changes and Psychological Outcomes

Pearson's correlations between CBF changes in brain regions where the two-way rmANOVA detected a significant interaction (i.e., the ACC) and changes in stress perception, trait anxiety, and flow experience were assessed. Pearson's correlations were corrected for multiple comparisons using the Holm's method (Holm, 1979). Python programming language was used to perform correlation analysis and illustrations.

Chapter 4

Results

4.1 Behavioural Results

4.1.1 Psychological Questionnaires

Results of questionnaires are shown in Figure 4.1. The two-way mixed ANOVA of perceived stress and mindfulness did not yield significant interactions; however, supporting our hypotheses, a significant reduction of stress levels [$t_{stress}(36) = 2.25$, $p = 0.03$, Cohen's d = 0.46)] in addition to a slightly increase in perceived mindfulness, were present in the experimental group (albeit with small effect sizes) compared to the control group, where no effects were seen [$t_{stress}(36) = 1.20$, $p = 0.24$, Cohen's d = 0.06)]. A significant interaction [$F(1,68) = 5.52$, $p = 0.02$] was seen in the two-way mixed ANOVA of trait anxiety. Post-hoc t-tests confirmed a significant decrease in trait anxiety [$t(35) = 3.29$, $p = 0.002$] in the experimental group, this significant decreased was not seen in the control group [$t(34) = 0.80$, $p = 0.43$, Cohen's d = -0.28]. Unpaired t-tests in the change of trait anxiety among both groups also revealed a significantly decreased in trait anxiety in the experimental group in which a large effect size was observed ($t(68) = 2.35$, $p = 0.02$, Cohen's d = -1.30). The two-way mixed ANOVA of physical well-being did not yield a significant interaction, and while a moderate effect (Cohen's d = 0.52) in improved physical well-being was observed in the experimental group, it was not statistically significant. A significant group by time interaction was, however, seen for the two-way mixed ANOVA of flow experience [F(1,51) = 9.254, p = 0.004]. Post-hoc paired t-tests showed a significantly increased flow experience for the experimental group [t(24) = -4.56, p = 0.0001] not seen in the control group [t(27) = -0.09, p = 0.93, Cohen's d = 0.04)]. Unpaired t-tests in the change of flow experience among both groups also revealed a significantly increased flow experience in the experimental group in which a large effect size was observed [t(51) = -3.04, p = 0.004, Cohen's d = 1.46]. Control and experimental group baselines were statistically different for the flow experience sample [t(51) = -3.24, p = 0.002] and for the trait anxiety sample [t(73) = 2.33, p = 0.02], with the experimental group scoring lower in flow experience and higher in the trait anxiety levels at baseline.

4.1.2 ANT Reaction Times

Results of the ANT reaction times for the two groups (control and experimental) that underwent fMRI scans are shown in Figure 4.2 and Figure 4.3. Strikingly, the mean overall reaction times improved by $\sim$ 48 ms and highly significant in the experimental group [t(1,19) = 5.07, p = 0.00008], while they only increased $\sim$ 23 ms in the control group; a change that was not significant [t(1,22) = 1.10, p = 0.285], i.e., there was more than a two-fold improvement in the experimental group compared to the control group. Nevertheless, a three-way interaction was not found to be significant for none of the three attention conditions. However, there was a significant two-way interaction [F(1,39) = 6.811, p = 0.01] between group and network condition (i.e., centered cue and spatial condition) for the orienting of attention. Post-hoc two-way ANOVA analysis revealed a significant main effect of group in the spatial cue condition [F(1,163) = 4.84, p = 0.03]. Furthermore, and not surprisingly, main effects of network condition were also seen for the alerting condition (no cue vs. centered cue) [F(1,39) = 11.097 , p =

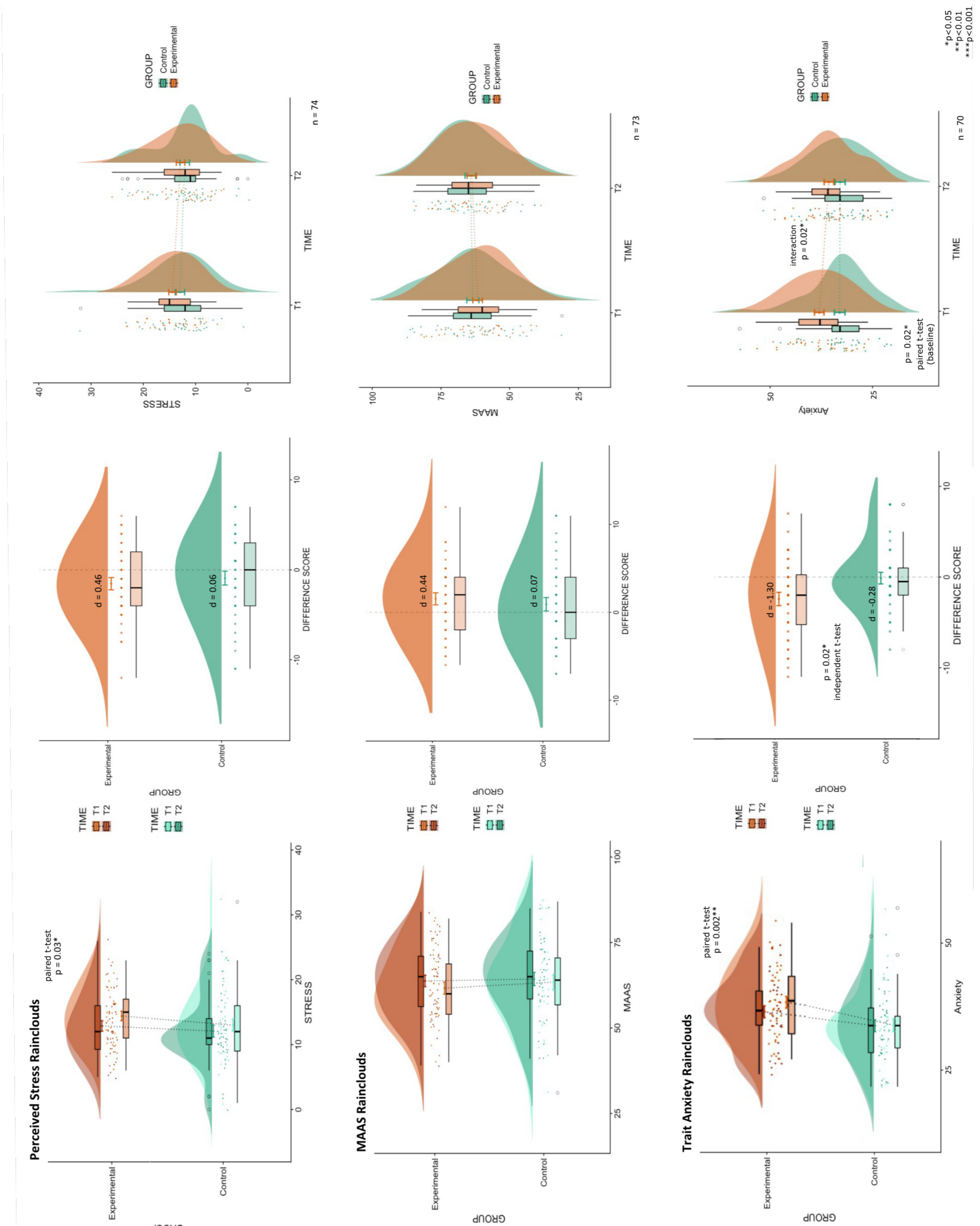

Figure 4.1: Rain-Cloud Plots of Psychological Outcomes. Significant p-values (p), Cohen's d effect sizes (d), and sample size (n) are shown.

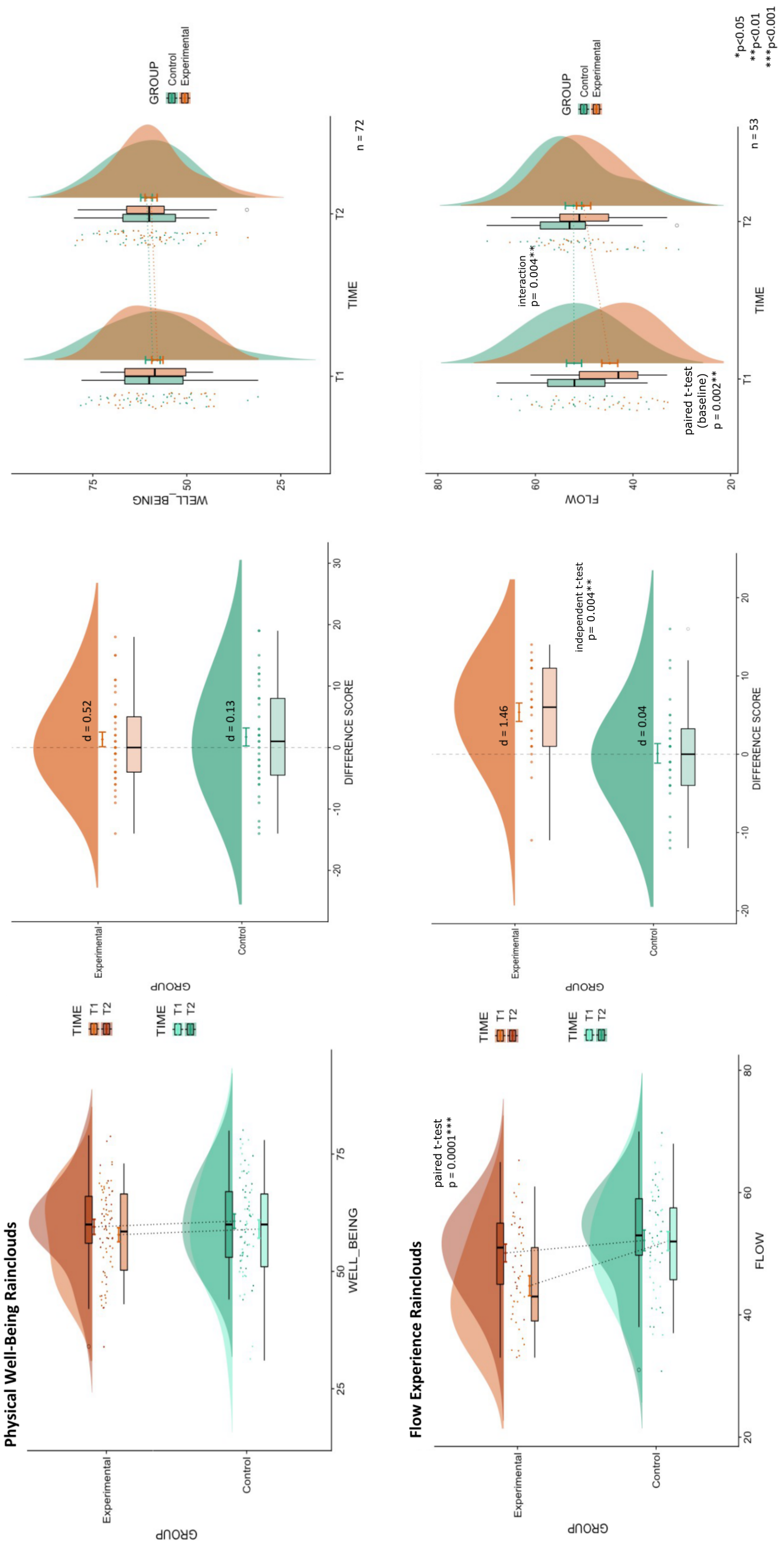

Figure 4.1: Continued.

0.002] and executive condition (incongruent vs. congruent)[$F(1, 40) = 34.39$, $p < 0.001$], indicating that the more complex condition required longer reaction times. As expected, main effects of time were seen for each of the attention condition [$F(1, 39)_{Alerting} = 16.469$, $p < 0.001$; $F(1,39)_{Orienting} = 21.16$, $p < 0.001$; $F(1,40)_{Executive} = 15.53$, $p < 0.001$], indicating practice effects.

As can be seen from the effect sizes per condition for the difference in reaction times between the two timepoints in each group in Table 4.1, the effects of the intervention were rather unspecific, in that reaction times strongly improved for the experimental group in all conditions, and therefore, no specific effect on any of the attention networks could be seen. Also, the impact of the training in accuracy was not able to be measured, as strong ceiling effects were present in both groups.

Table 4.1: ANT effect sizes per condition reflecting the difference in reaction times between the two timepoints for each group.

Cue	Target	Cohen's d*	
		CON	EXP
NO	C	0.24	2.3
	I	0.40	3.2
CENTER	C	0.46	3.1
	I	0.26	3.3
SPATIAL	C	0.78	1.4
	I	0.43	3.9

C = congruent; I = incongruent

*The Cohen's d (d) effect size scale is: negligible effect ($d < 0.2$), small effect ($0.2 \leq d < 0.5$), moderate effect ($0.5 \leq 0.8$), and large effect ($d \geq 0.8$) (Cohen, 1988, 1992).

4.2 Imaging Results

4.2.1 fMRI Results

4.2.1.1 Imaging of Attentional Networks

Figure 4.4 shows the results of a sample t-test including all participants to see the activation of the alerting network of attention and a comparison with previous

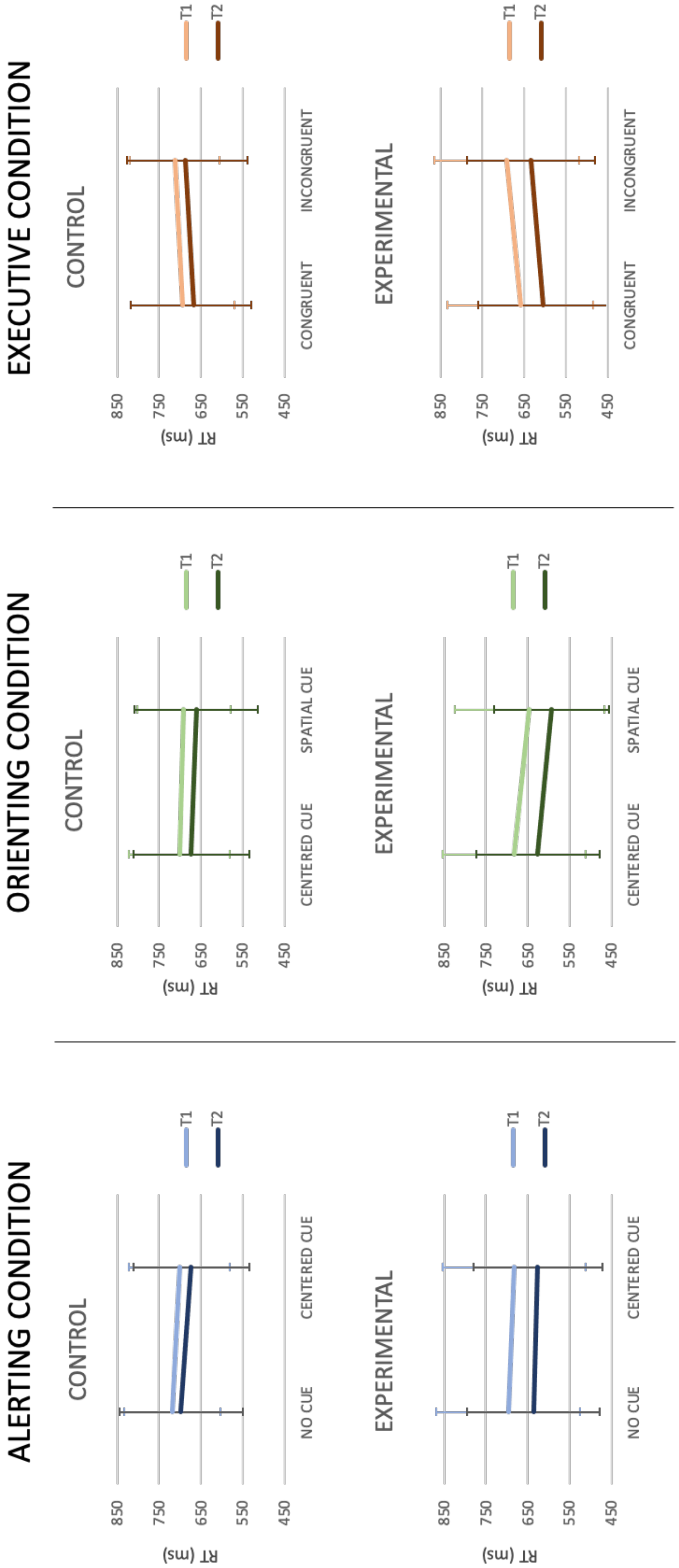

Figure 4.2: ANT Reaction Times (mean ± SD) in ms of the control and experimental groups before and after the intervention.

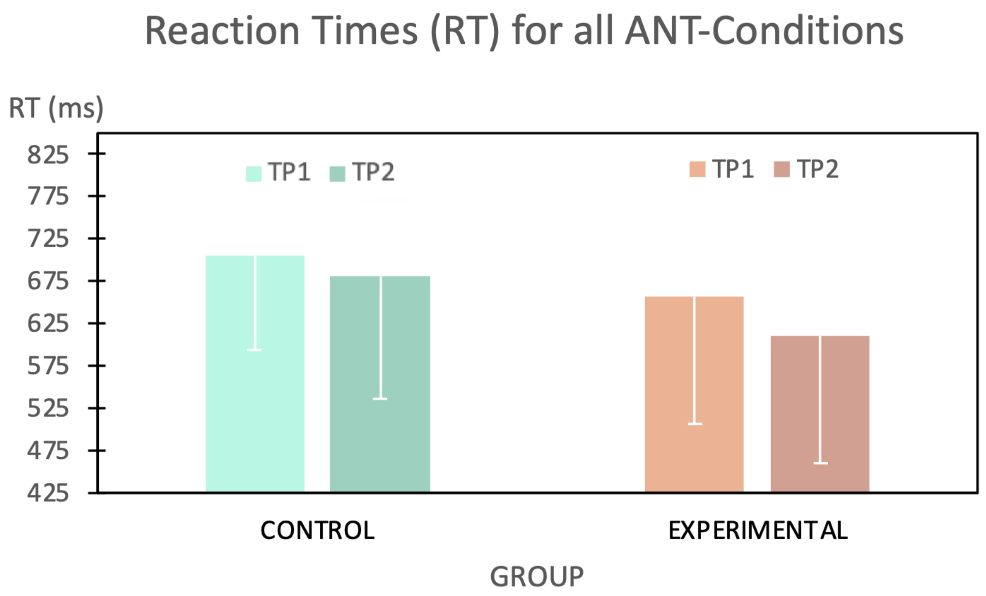

Figure 4.3: ANT Mean Reaction Time (mean ± SD) in ms of the control and experimental groups before and after the intervention over all conditions.

literature. Figure 4.5 shows the results of a sample t-test including all participants to see the activation of the orienting network of attention and a comparison with previous literature. And, Figure 4.6 shows the results of a sample t-test including all participants to see the activation of the executive network of attention and a comparison with previous literature. Reproducibility of the imaging of the attentional networks as in Fan et al. (2005) was only possible for the alerting network of attention (see Figure 4.4).

4.2.1.2 Imaging Results of the Two-way Repeated-Measures Factorial ANOVA

Results of the whole brain two-way repeated-measures factorial ANOVA (see Figure 4.7 and Table 4.2) demonstrated a significant training-associated increase in activation in the superior frontal gyrus (SFG), Brodmann area 31 or PCC, and the right hippocampus in the experimental group compared to the control group for

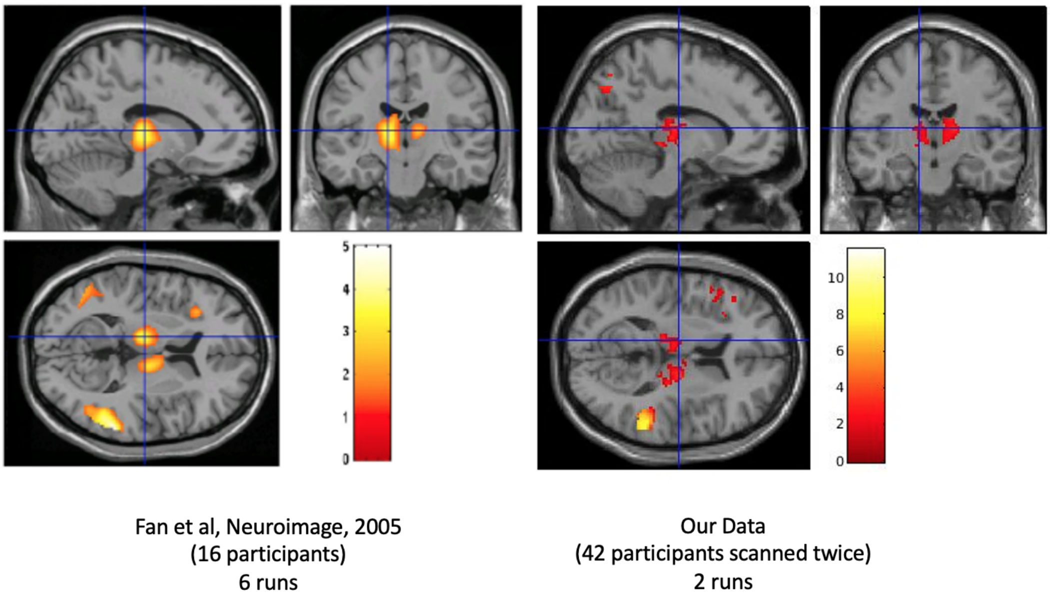

Figure 4.4: Alerting Network of Attention. Masked regions: right superior temporal gyrus, brain stem, thalamus, parietal lobe, left fusiform, left inferior frontal gyrus, vermis 6. Licence Number: 5271351122300 given by Elsevier and the Copyright Clearance Center (CCC) to reuse and adapt Figure 2 of Fan et al. (2005) for this thesis.

the alerting condition. Post-hoc t-tests did not show significant results in these areas; however, box plots (see Figure 4.8) of the parameter estimates of the activated regions showed decreased activation in the control group and increased activation in the experimental group after the intervention training in the aforementioned three brain regions. The other attention conditions (i.e., orienting and executive attention) showed no significant interaction results.

4.2.2 DTI of the Right UNC and SLF

Results of the two-way rmANOVAs via JASP showed a significant training-associated increased in FA in the right UNC [$F(1,42) = 6.047$, $p=0.018$] of the experimental group compared to the control group (see Figure 4.9), which survived Bonferroni correction. Results of the two-way rmANOVA on the SLF yielded no significant interaction. Increased FA values in the right uncinate fasciculus might indicate

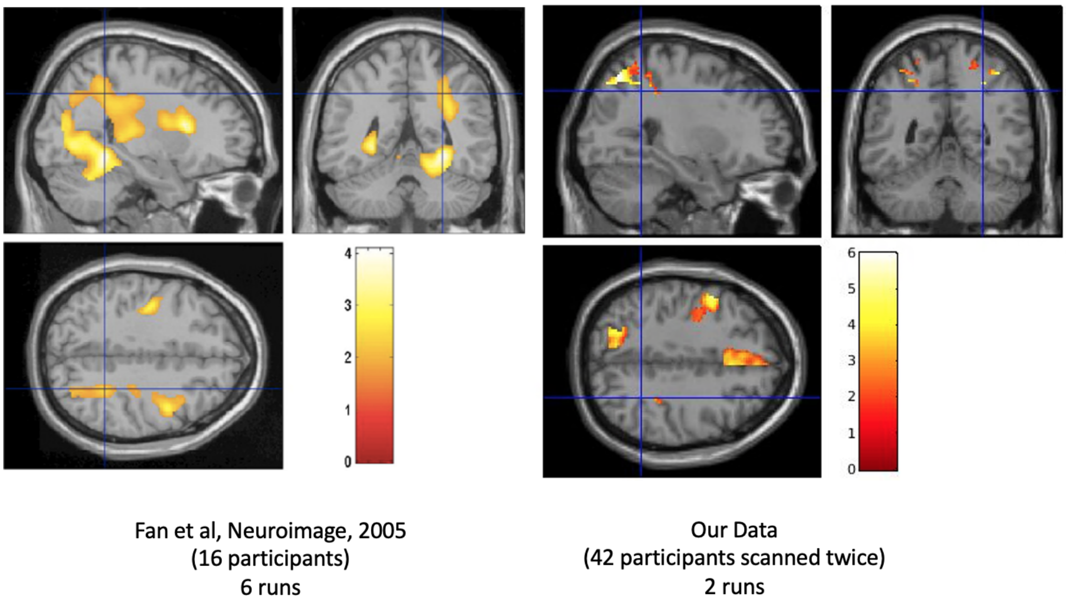

Figure 4.5: Orienting Network of Attention. Masked regions: fusiform gyrus, left precental gyrus, superior parietal lobe, left superior frongal gyrus, right post-central gyrus. Licence Number: 5271351122300 given by Elsevier and the Copyright Clearance Center (CCC) to reuse and adapt Figure 2 of Fan et al. (2005) for this thesis.

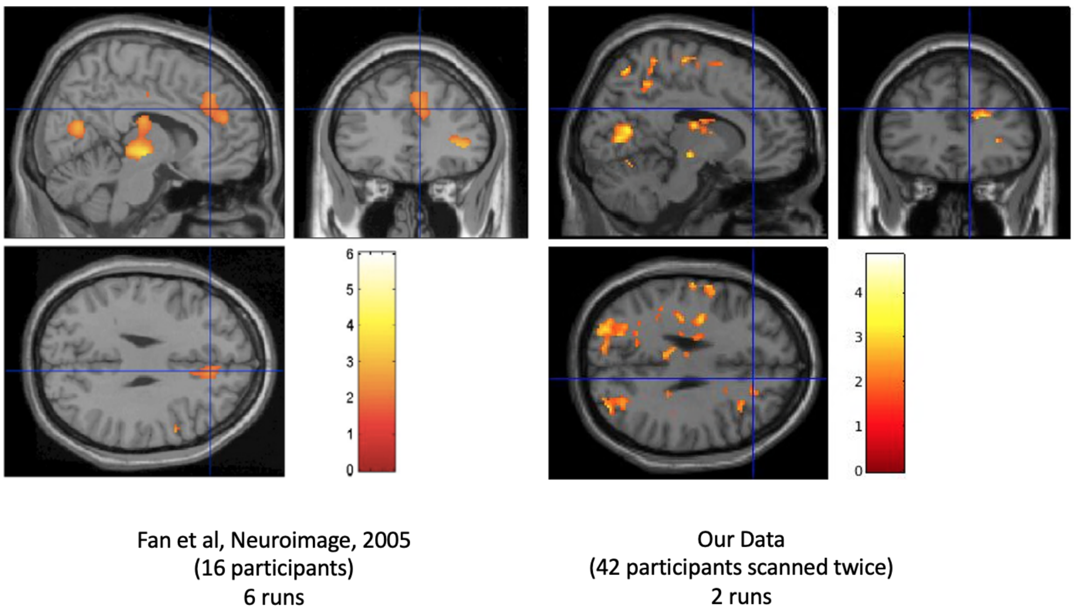

Figure 4.6: Executive Network of Attention. No masked regions. Licence Number: 5271351122300 given by Elsevier and the Copyright Clearance Center (CCC) to reuse and adapt Figure 2 of Fan et al. (2005) for this thesis.

Table 4.2: Regions showing a significant group-by-time interaction for the alerting condition of the ANT (no cue minus center cue).

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

k = cluster size in voxels

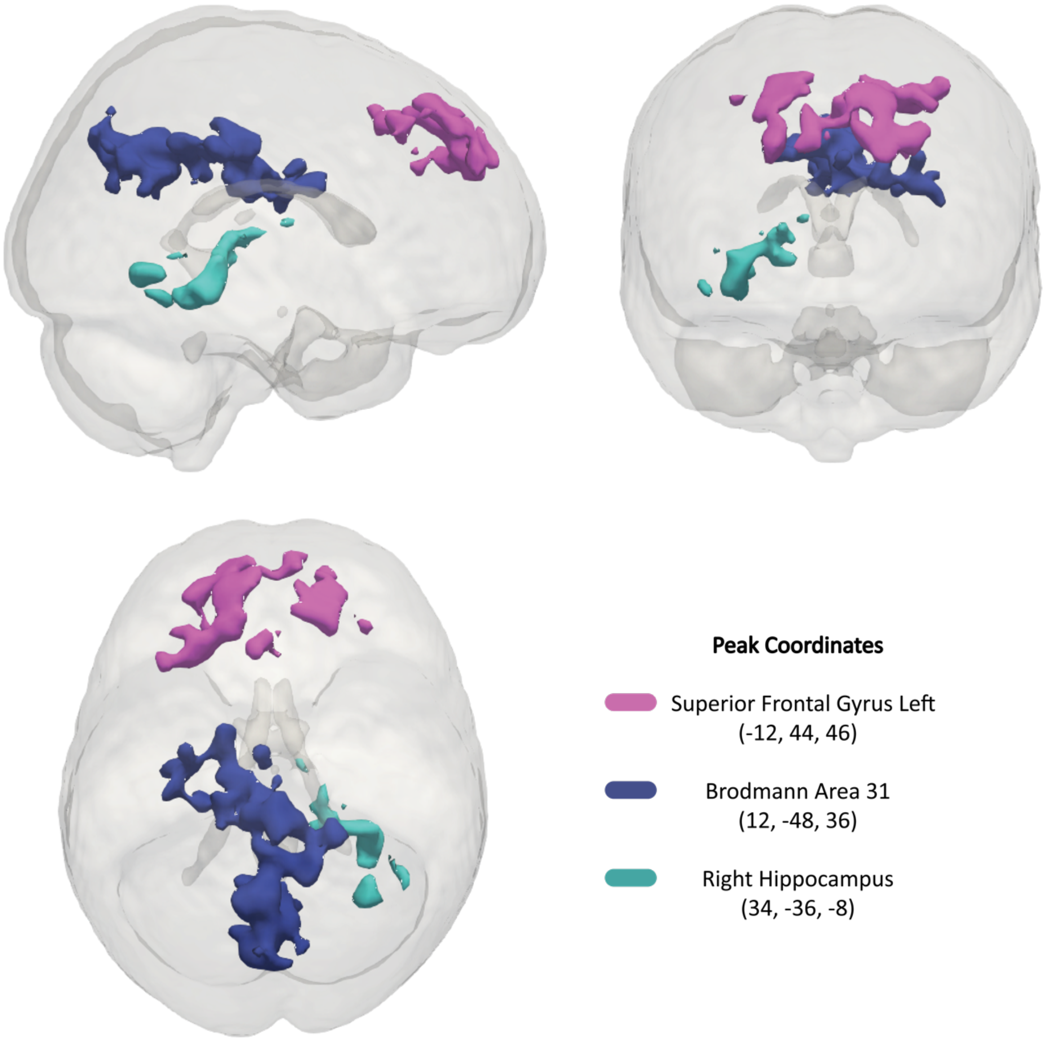

Figure 4.7: fMRI neuroimaging results of the significant interaction of the two-way repeated measurements factorial ANOVA of the alerting network of attention.

increased connectivity between the right hippocampus and frontal areas of the brain. Figure 4.10 and Figure 4.11 show an example of the right UNC for one control and experimental participant after the training, respectively.

4.2.3 Perfusion Imaging With ASL

Global CBF values in GM of the control and experimental groups are reported in Table 4.3. Results of the two-way rmANOVAs on global CBF yielded no significant

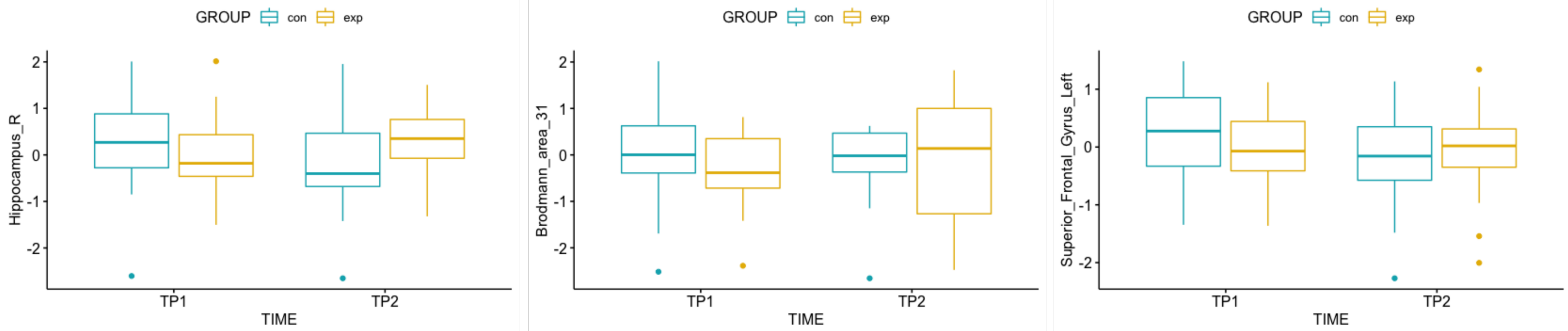

Figure 4.8: fMRI parameter estimates boxplots illustrating the directionalities of activation in the left superior frontal gyrus, Brodmann area 31, and right hippocampus of the control and experimental group for the two time-points (before and after the intervention).

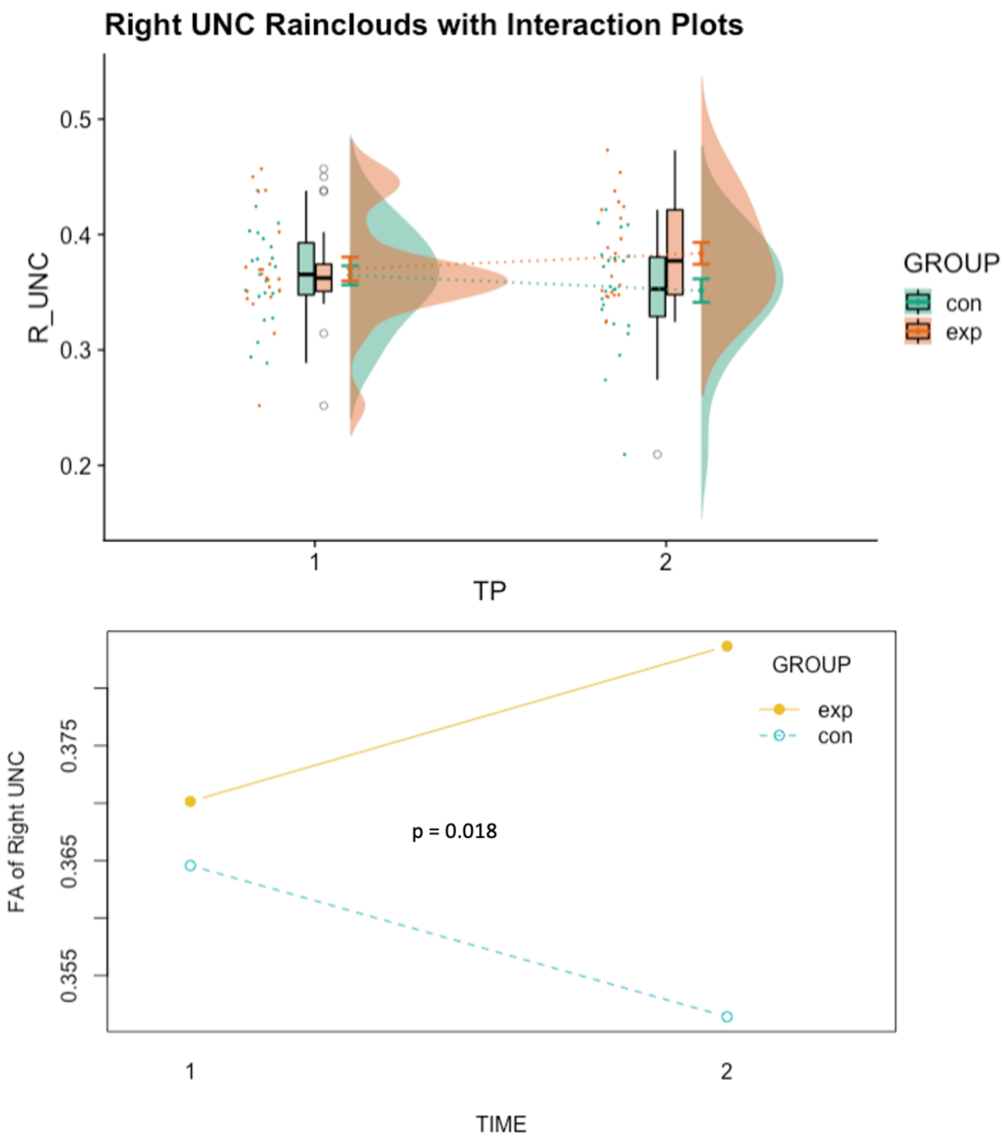

Figure 4.9: UNC FA Rain Cloud and Interaction Plot

interactions. Figure 4.12 and Figure 4.13 show an example of the calculated CBF maps for one control and experimental participant, respectively.

However, in the ROI analysis, results of the two-way rmANOVAs showed a significant training-associated decrease in CBF in the left thalamus [F(1,40) = 5.01, p = 0.031] and ACC [F(1,38) = 8.29, p = 0.007] of the experimental group compared to the control group (see Figure 4.14). Post-hoc paired t-tests showed no significant differences for the control group [$t_{leftThalamus}(21)$ = -0.98, p = 0.34; $t_{ACC}(21)$ =

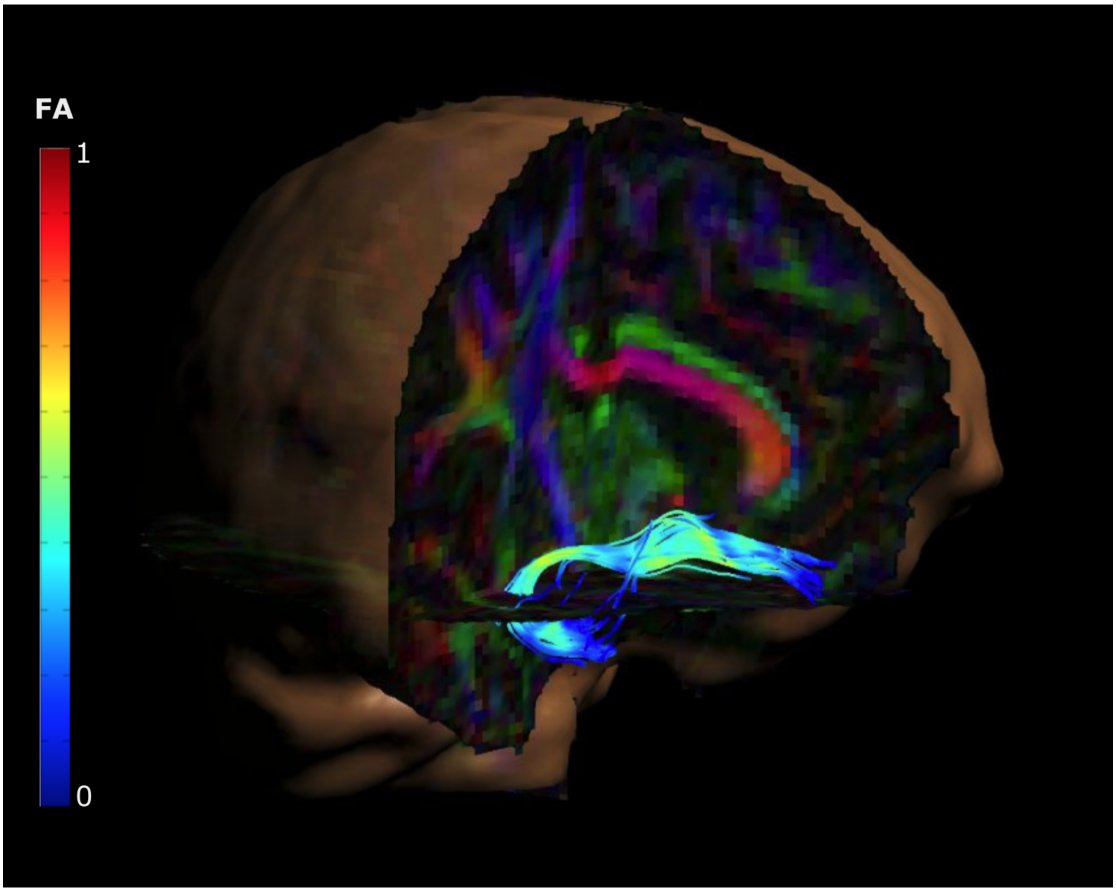

Figure 4.10: Tractography of the right UNC of a participant in the control group after the health-enhancement training (female, age: 23 years old).

Table 4.3: Global GM CBF values of our participants before and after the intervention

Group	Time Point	CBF (mean ± sd) *(ml/100g/min)*
Control	before	37.4 ± 7.3
Control	after	38.2 ± 7.3
Experimental	before	38.3 ± 7.4
Experimental	after	35.1 ± 7.0

3 outliers were removed.

-0.99, p = 0.33], but a decreased CBF in the experimental group after the training [$t_{leftThalamus}(19) = 2.30$, p = 0.033; $t_{ACC}(17) = 3.00$, p = 0.008].

Control and experimental group baselines were not statistically different for the ACC and left Thalamus CBF measurements. The significant interaction in the

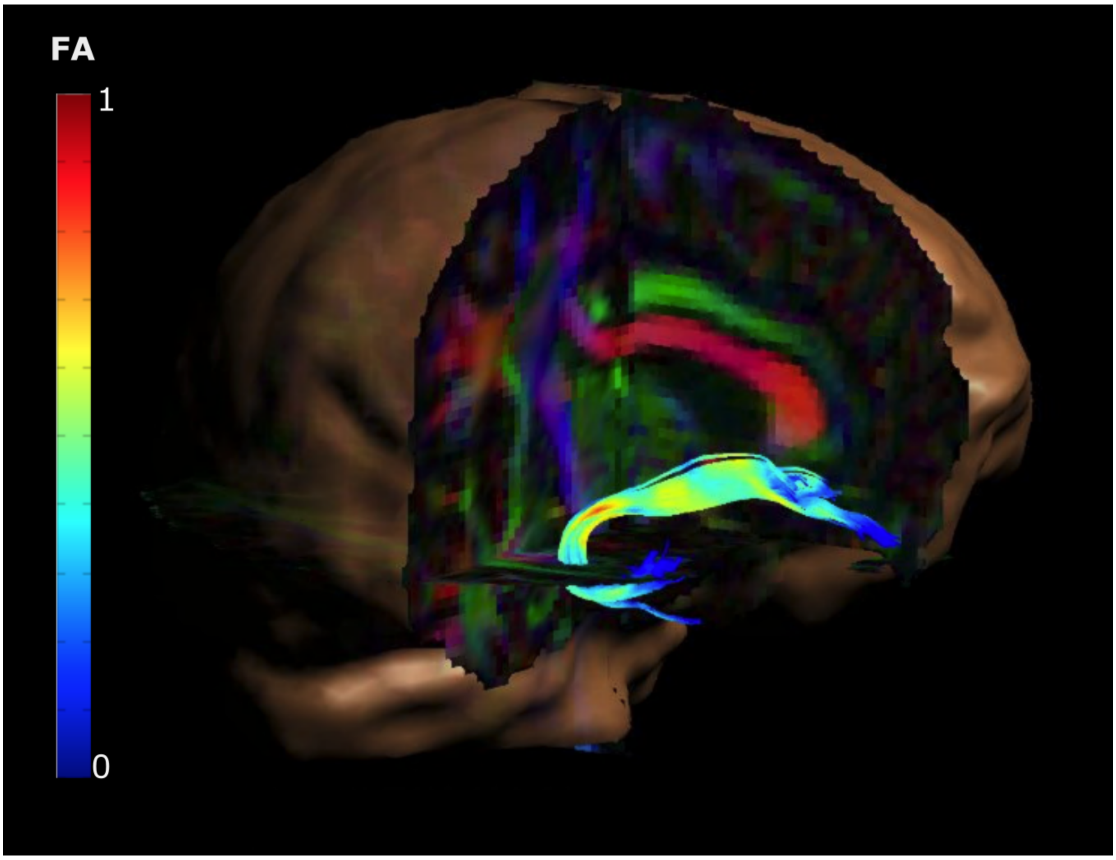

Figure 4.11: Tractography of the right UNC of a participant in the experimental group after the mindfulness training (male, age: 32 years old).

ACC marginally survived the Bonferroni correction, while the significant interaction in the left thalamus did not. Results of the two-way rmANOVAs for the rest of the analysed regions (i.e., frontal lobe, superior parietal lobule, insula, putamen, caudate, right thalamus, and right amygdala) showed no significant interactions.

4.2.4 Others: Voxel-Based Morphometry (VBM) and Resting-State fMRI Analyses

Results of the VBM analysis generated based on the T1-weighted images and resting-state fMRI are reported elsewhere [Julia Schulz, Master Thesis; Bremer et al. (2022)].

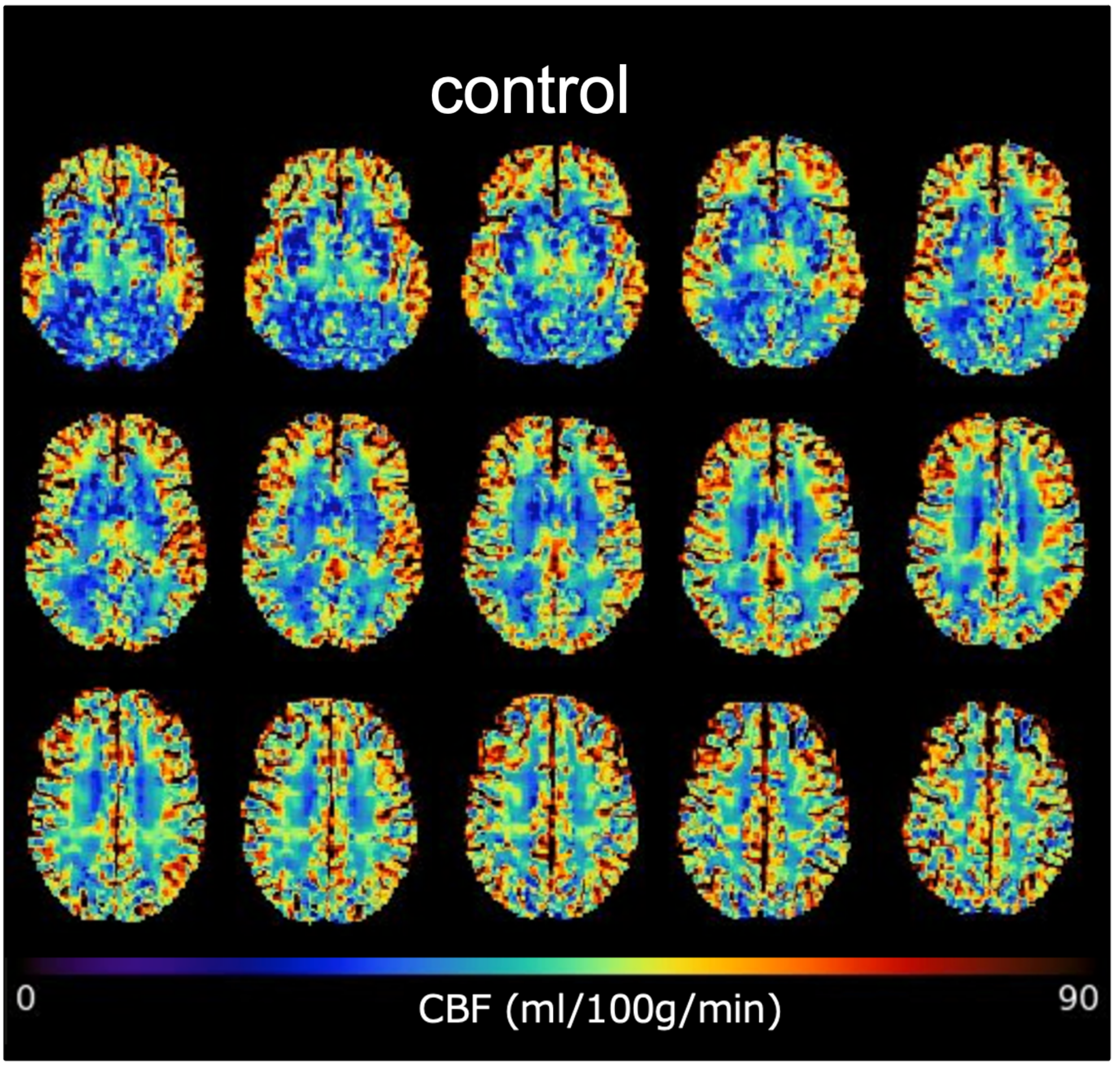

Figure 4.12: CBF maps of a participant in the control group after the health-enhancement training.

4.3 Correlations Between Brain Activations in the Alerting Network of Attention, ANT Reaction Times, and Pyschological Outcomes

There was a significant negative correlation (r = -0.51, p = 0.02) between PSS scores and the activation in the right hippocampus after the mindfulness intervention in the experimental group, that marginally survived the Holm's correction method for multiple comparisons (see Figure 4.15). This correlation was not seen

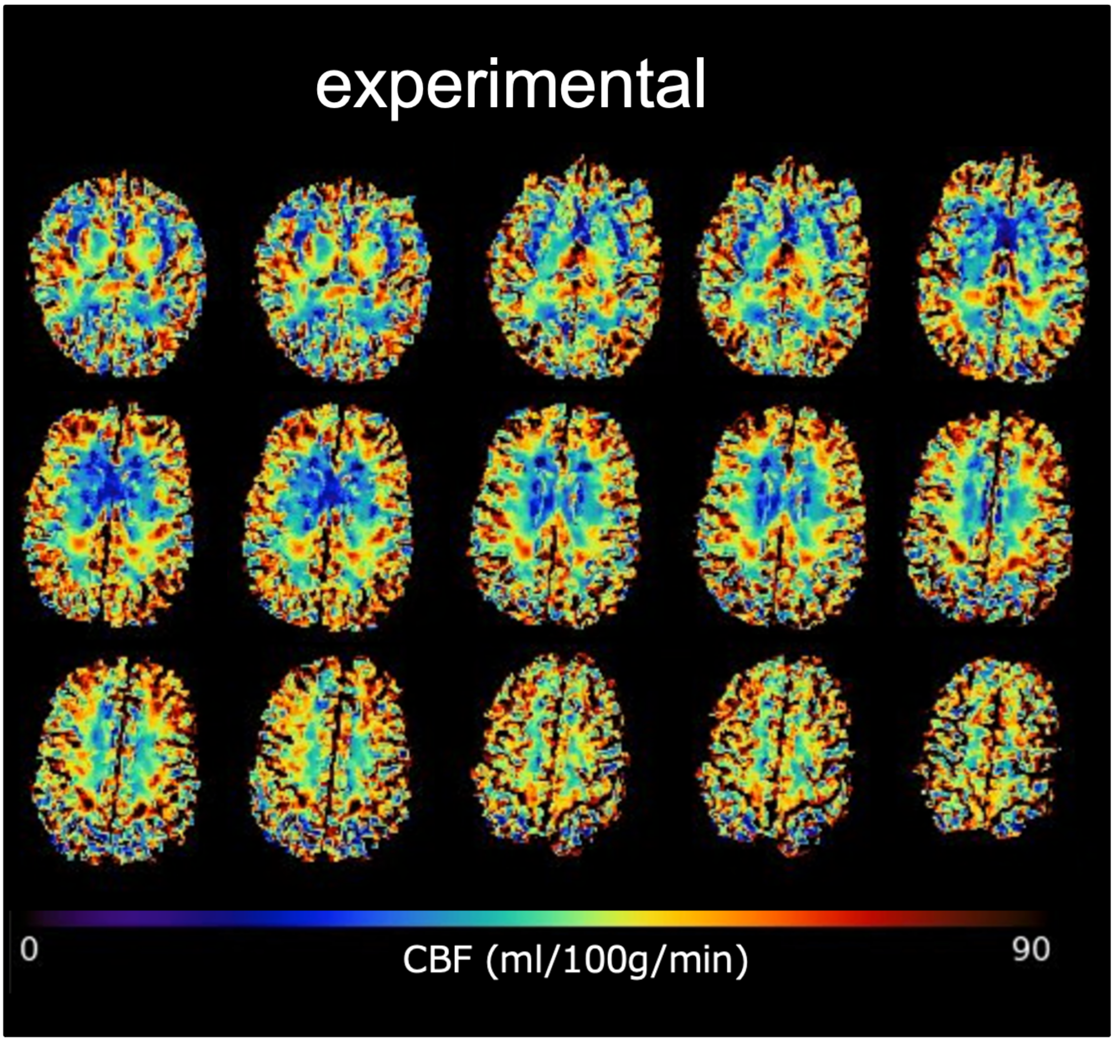

Figure 4.13: CBF maps of a participant in the experimental group after the mindfulness training.

in the experimental group before the intervention nor in the control group at any of the two timepoints (see Figure 4.16). The correlation between the change in PSS scores and change in mean ANT reaction times in the experimental group (r = 0.36, see Figure 4.17) slightly missed significane (p = 0.059, one-tailed). There was no significant correlation between ANT Reaction Times and the PSS scores nor between the Alerting Effect (no cue – centered cue) and the activated brain regions (SFG, Brodmann area 31, and right Hippocampus) before and after the intervention. However, there was a positive correlation (r = 0.42, see Figure 4.18

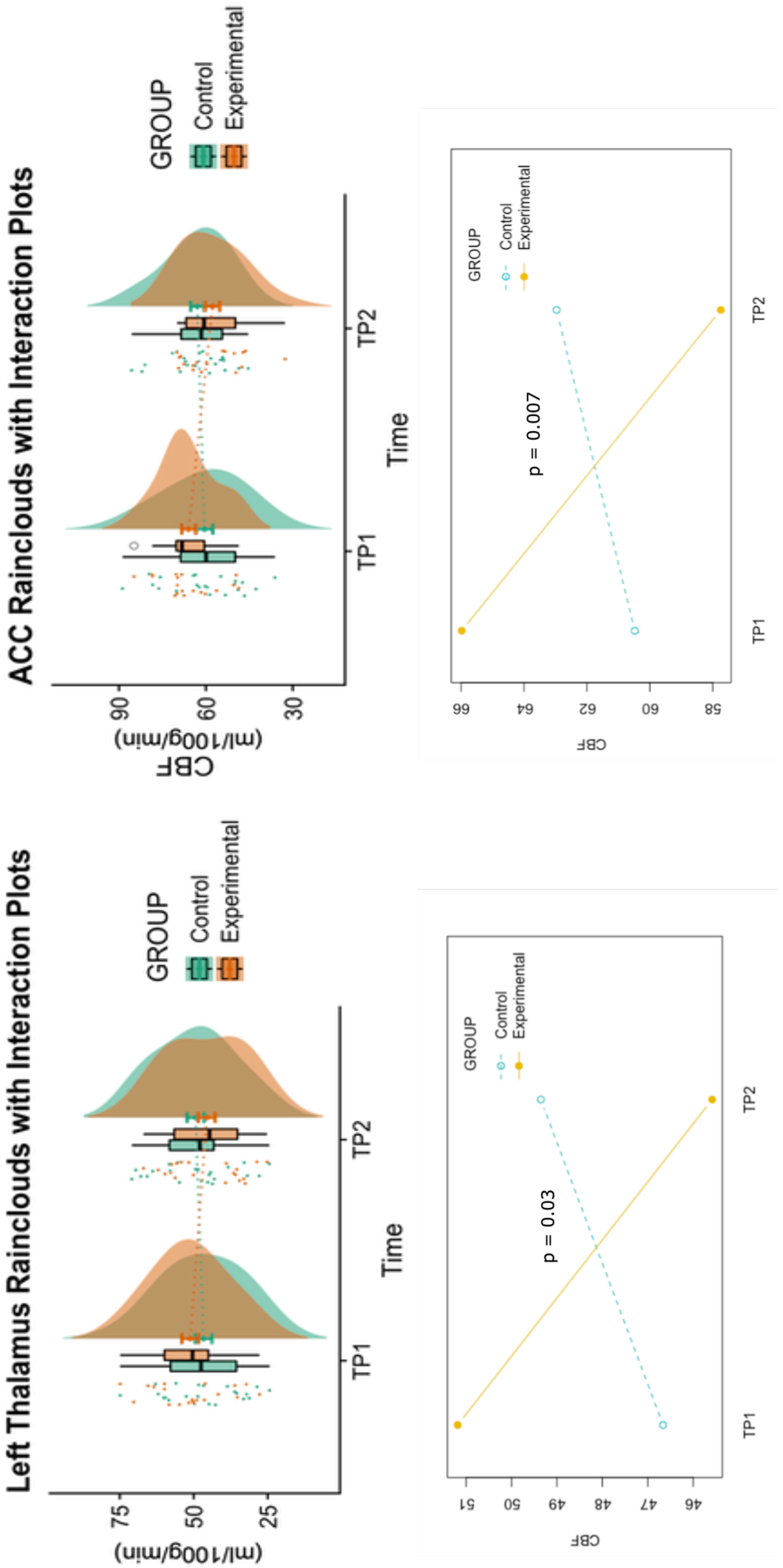

Figure 4.14: CBF rainclouds of ROIs with significant two-Way rm-ANOVA interactions.

between the percentage change in activation at the SFG and the change in reaction times of the centered cue condition that missed significance (p = 0.07) in the experimental group, not seen in the control group.

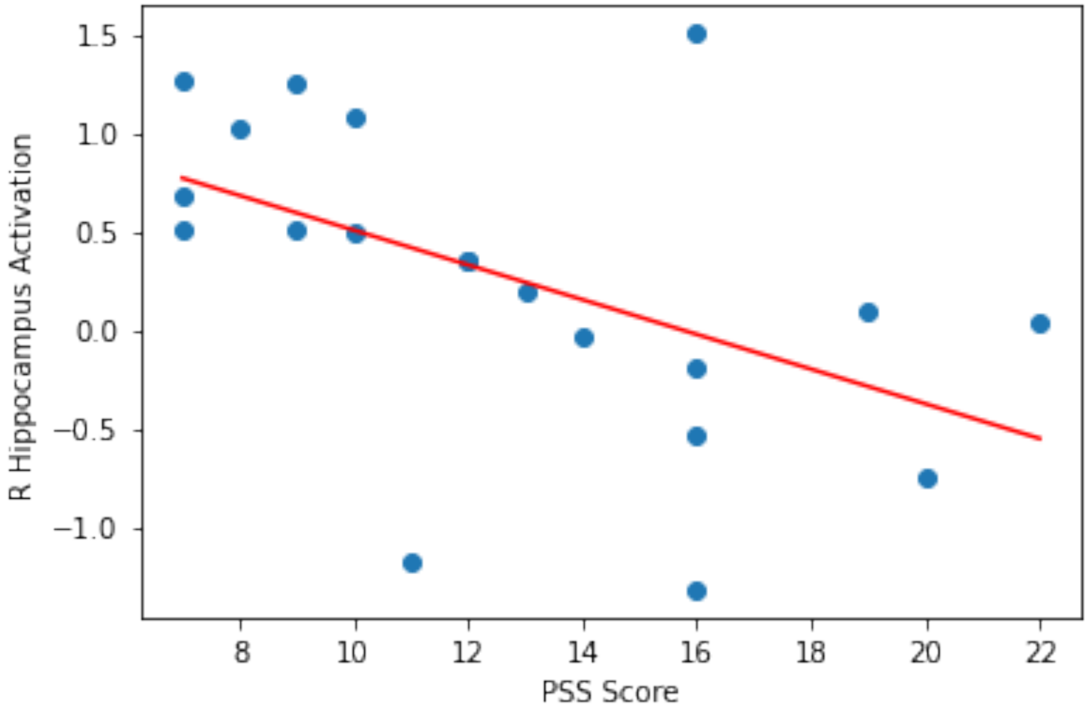

Figure 4.15: Correlation between PSS scores and the right hippocampus after the mindfulness training.

A significant positive correlation (r = 0.52, p = 0.02) was found between trait anxiety scores and the activation in the right hippocampus in the control group before the intervention, this correlation was not seen after the intervention and neither in the experimental group before the mindfulness training. However, a significant negative correlation (r = -0.46, p = 0.04) was found in the experimental group after the training (see Figure 4.16). The correlation in the control group marginally survived Holm's correction, while the correlation in the experimental group did not.

Significant positive correlations between flow experience measurements and right hippocampus (r = 0.49, p = 0.047), Brodmann area 31 (r = 0.64, p = 0.006), and SFG (r = 0.6, p = 0.01) were found in the experimental group after the mindfulness intervention in the alerting condition. These correlations were not seen in the experimental group before the intervention nor in the control group at any of the two timepoints (see Figure 4.16). These previous correlations survived Holm's correction for multiple comparison.

No significant correlations were found between trait anxiety and overall ANT reaction times, nor between flow experience and overall ANT reaction times (see Figure 4.17).

4.4 Correlations Between Psychological Outcomes, ANT RTs, and FA Values in the Right UNC

No statistically significant correlations were found between the change in FA values in the right UNC and the change in perceived stress, trait anxiety, flow experience, and ANT RT between the control nor the experimental group (see Figure 4.19).

4.5 Correlations Between Psychological Outcomes and CBF Values in the ACC

Figure 4.20 shows a significant positive correlation ($r = 0.43$, $p = 0.045$) between the percentage change of perceived stress and the percentage change in CBF values in the ACC in the control group, not seen in the experimental group ($r = 0.13$, $p = 0.62$). When accounting for multiple comparisons, this correlation did not survived the Holm's correction. No significant correlations were found between trait-anxiety and CBF in the ACC, nor between flow experience and CBF in the ACC.

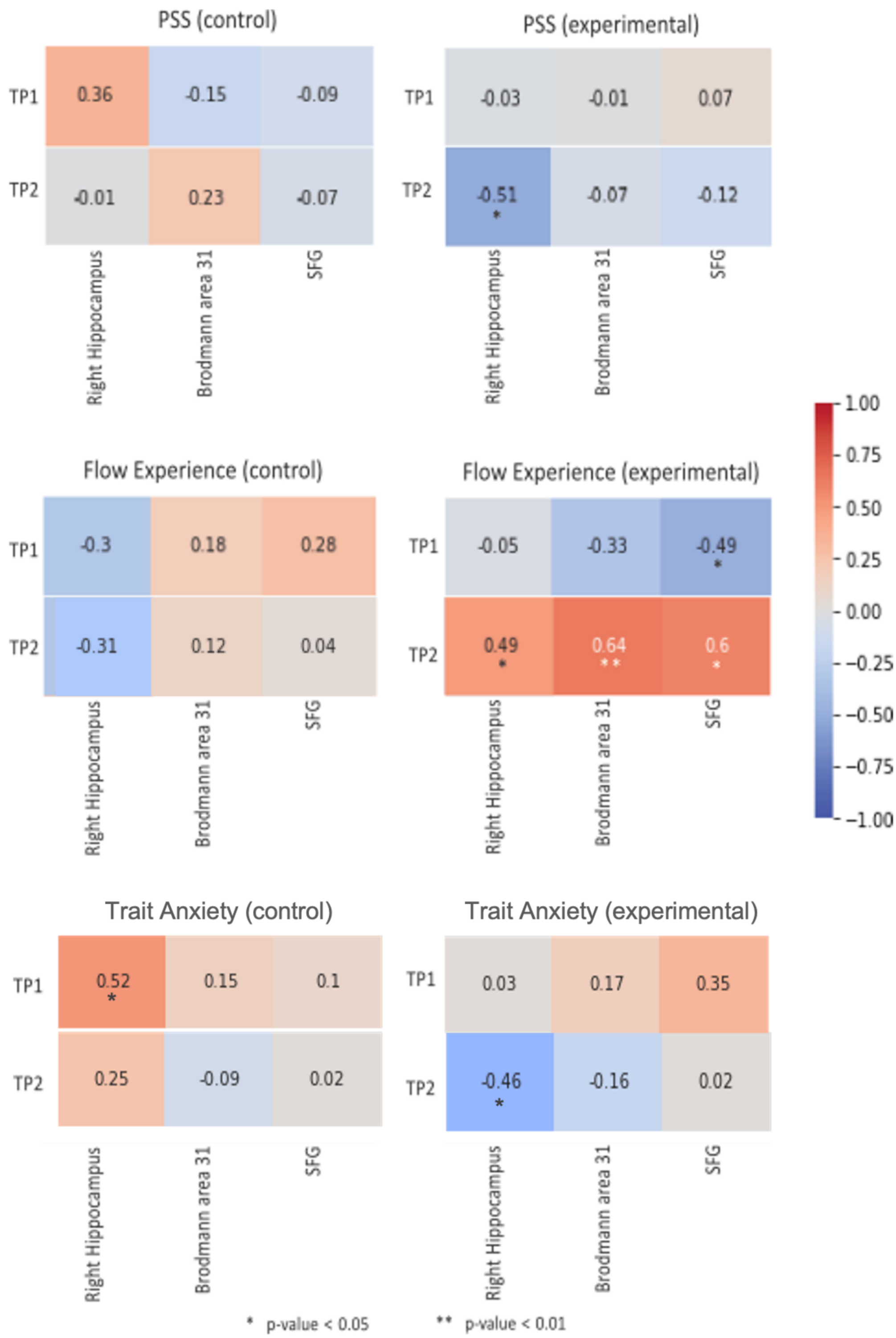

Figure 4.16: Correlation between PSS, flow experience, trait anxiety, and brain activations accross the different time points and for the control and experimental groups.

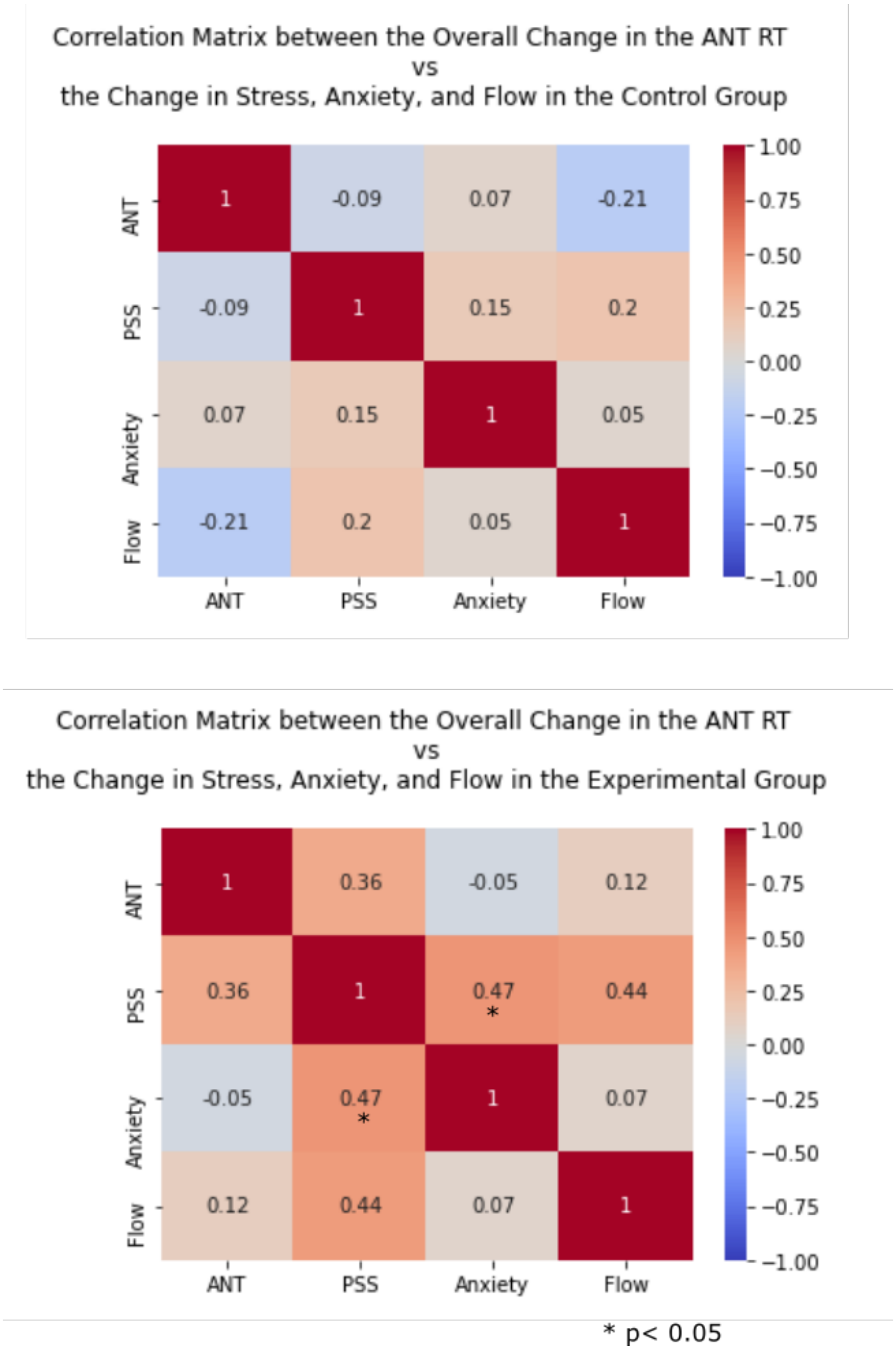

Figure 4.17: Correlation between PSS, flow experience, trait anxiety, and ANT reaction times across the different time points and for the control and experimental groups.

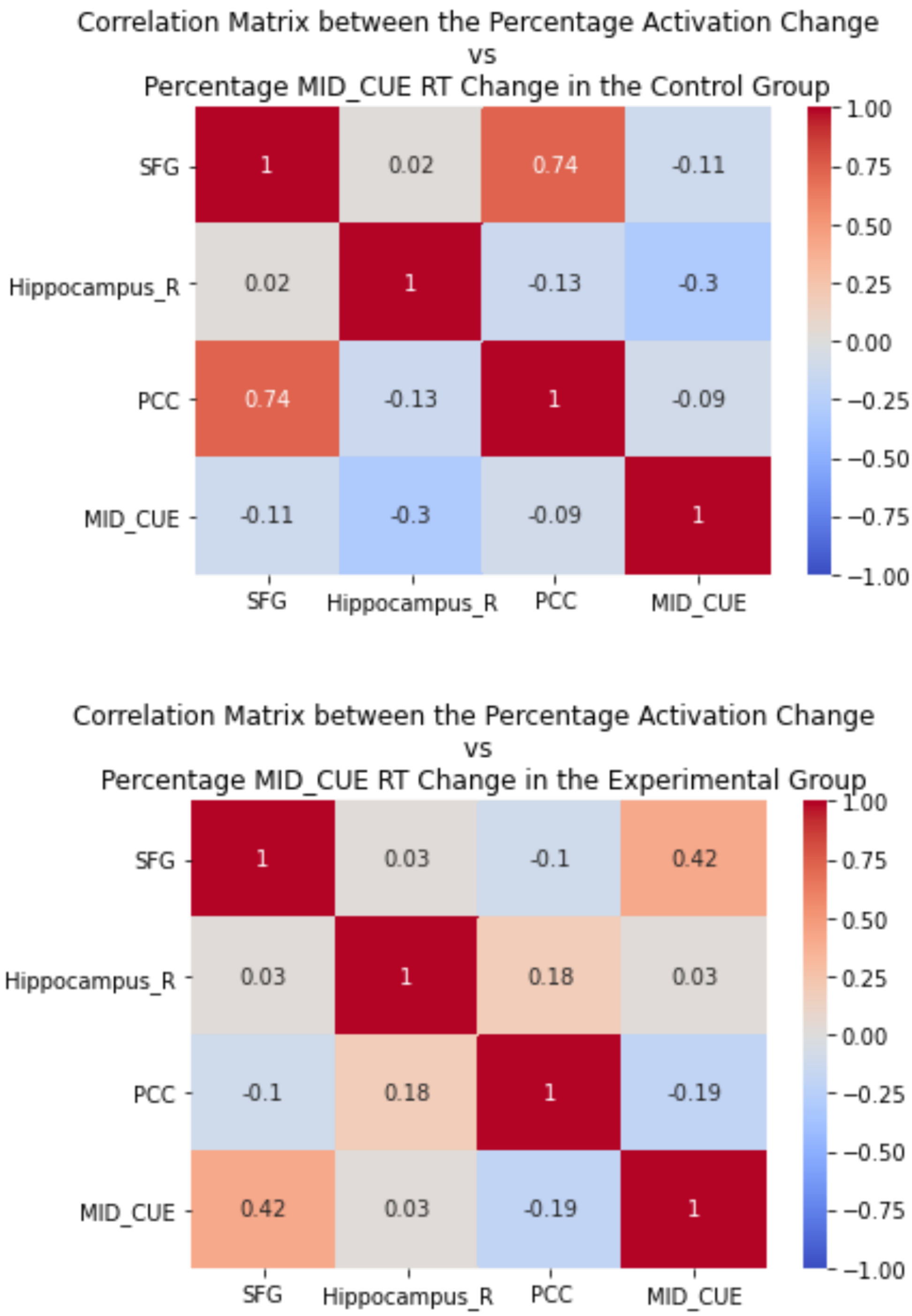

Figure 4.18: Correlation between the percentage change in brain activations and percentage change of the reaction times of the alerting cue for the control and experimental groups.

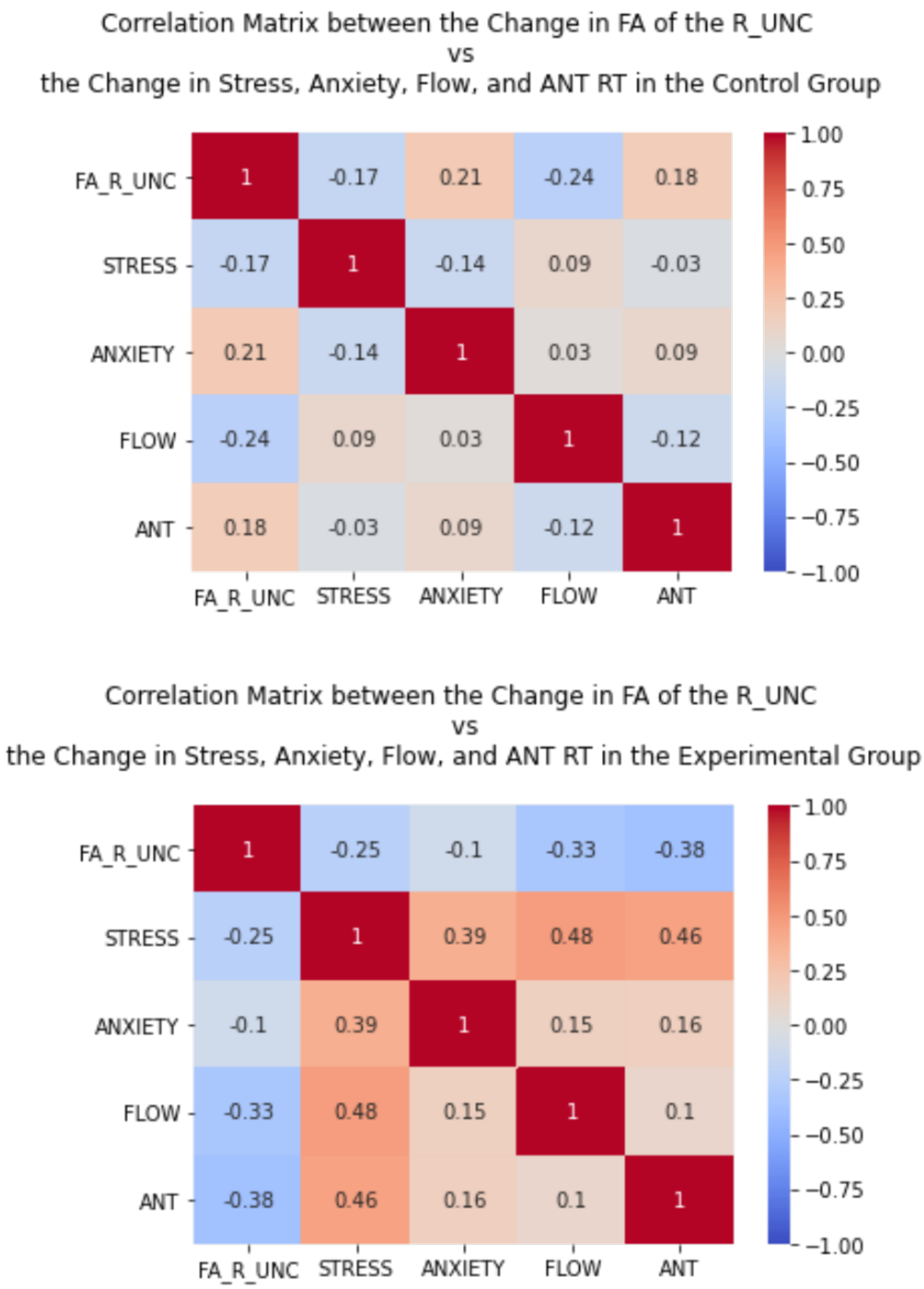

Figure 4.19: Correlation between changes in stress, trait anxiety, flow experience, ANT RT and changes in FA in the right UNC of the control and experimental groups after the intervention.

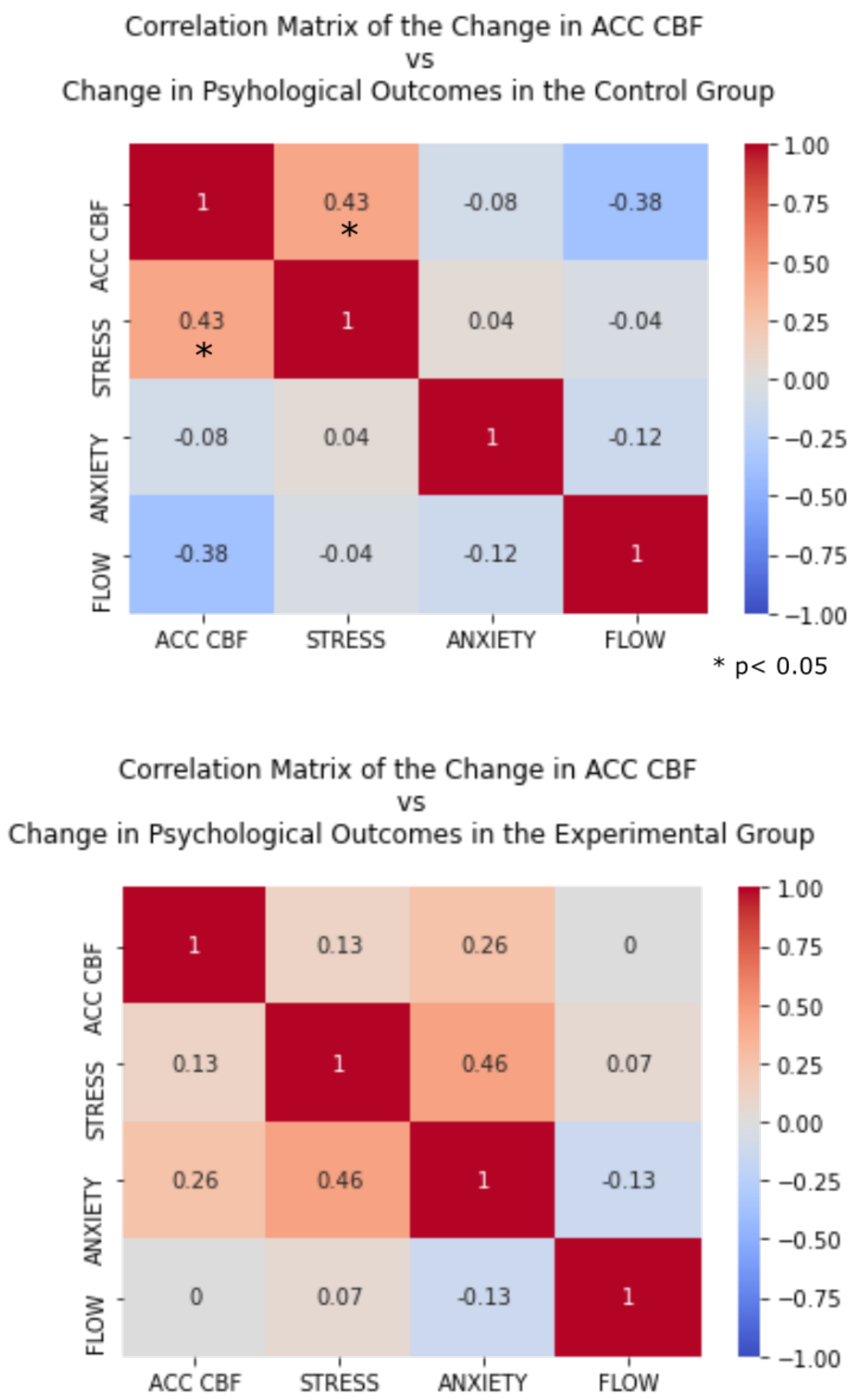

Figure 4.20: Correlation between changes in stress, trait anxiety, and flow experience and changes in CBF in the ACC in the control and experimental groups after the intervention

Chapter 5

Discussion

5.1 Summary of Findings

This study demonstrated that, compared to an active control health-enhancement training, a 31-day online mindfulness meditation training that required relatively little time of the participants per day (about 15 mins) led to greater improvements in measures of mental health (i.e., reductions in anxiety and stress levels), state of mind (i.e., increased flow experience), and attentional performance.

On the neuronal level, it led to stronger brain activation in the PCC, left superior frontal gyrus, and right hippocampus during the alerting condition of attention of the ANT. PCC, right hippocampus, and SFG activations in the experimental group were positively correlated with flow experience, and only the right hippocampus activation in the experimental group was negatively correlated with stress and anxiety. Increased FA in the right UNC, and decreased CBF in the ACC were also seen in the experimental group as a result of the mindfulness training.

5.2 ANT fMRI, Psychological Outcomes, and FA Changes

In my study, I found that upon completing a 31-day online mindfulness training course, improvements in attentional performance in addition to an increased activation in the left superior frontal gyrus, Brodmann area 31 (PCC), and right hippocampus could be observed. A significant group by time interaction was found for the trait anxiety, in which anxiety levels were reduced after the mindfulness training. Paired t-tests of decreased stress levels, decreased anxiety, and increased flow experience reached statistical significance in the experimental group. Eventhough not statistically significant, small and moderate effects in improving mindfulness and physical well-being were observed respectively, after the mindfulness training had been completed.

Although the group by time interaction in perceived stress was not significant - most probably due to the short duration of our training and the stress baseline of our participants - there was a significant decrease in perceived stress levels in the experimental group after the mindfulness training, not seen in the control group. Previous MBSR-studies have also shown that psychological outcomes can be positively moderated by the number of treatment/training hours (Khoury et al., 2015; Sedlmeier et al., 2018); therefore, as the present mindfulness training was very short compared to the standard MBSR program, I expect that by increasing the duration of our training, larger effects on the observed variables could be obtained. However, the moderation of baseline characteristics on intervention responses should also be considered, as it has been shown that individuals with high distress levels show larger changes (i.e., high-distressed individuals are more sensitive to mindfulness trainings) than well-functioning individuals that undergo the same amount of training hours (Rosenkranz et al., 2019).

The observed significant increase of flow experience in the experimental group was a very interesting finding. A recent study conducted by Xie (2021) on flow experience of members of a work team environment reported that the most proactive workers had higher team mindfulness and flow experience, and this same study found a positive correlation between flow experience and team mindfulness. The presented online mindfulness training may be very suitable for work environments as it increases individual flow experience which can enrich the working performance of members of a team. In addition, this increase in flow was positively correlated with increased activation in the right hippocampus, Brodmann area 31, and SFG. Although it is difficult to interprete these results, as the neurocognitive processes behind the state of flow are still an open area of research (van der Linden et al., 2021), these correlations indicate a close association between changes in activation and changes in mental state (i.e., with those subjects showing an increase in flow experience after the training exhibiting also an increase in brain activation).

Moreover, the behavioural results of the ANT showed larger improvements in most measures in the experimental group compared to the control group, thereby indicating that the mindfulness training positively affected attention and executive function.

On the neuronal level, our 31-day mindfulness training was associated with a significant increase in PCC, SFG, and right hippocampus activation during the alerting mode of attention. The PCC, which is considered to be a major hub of the default mode network has previously been associated to be an area of the brain that is very susceptible to the effects of mindfulness meditation (Bilevicius et al., 2018; Creswell, 2017; Kral et al., 2019; Mai & Paxinos, 2012). A recent fMRI cross-sectional study between regular meditators of attentional training meditation traditions (Zen, Kriya yoga, and mindfulness of breathing) and nonmeditators showed increased PCC activation during an adapted Stroop Word-Color Task (SWCT) (i.e., a sustained attention task) in the meditation practitioners, which goes in line with the increased activity seen in the PCC during our alerting condition (Rodrigues et al., 2018). While the PCC is connected to the DLPFC, the thalamus, and the hippocampus (amongst other brain regions), it additionally has strong connections to the anterior part of the CC, which is a region important for executive functions that has also been found to be susceptible to the effects of mindfulness meditation (Fox et al., 2016; Kwak et al., 2019; Pernet et al., 2021). In fact, there is also evidence that experienced meditators have an increased connectivity between the PCC, ACC and DLPFC (Brewer et al., 2011). This interplay of brain regions is relevant for several cognitive processes. Specially, the PCC is also known to play an important role in the frontoparietal control network in addition to the dorsal attention network, which are two networks critical for visuospatial attention (Leech & Sharp, 2014; Leech & Smallwood, 2019; Somers & Sheremata, 2013).

Similarly, our observed activations in the SFG, can be linked to previous findings which associate SFG activations with higher cognitive functions and, more specifically, with attentional shifting and spatial cognition (du Boisgueheneuc et al., 2006; Nagahama et al., 1999). Lesion studies have also been able to demonstrate longer reaction times in patients with SFG lesions in the Flanker Task (Usami et al., 2013). Therefore, our findings of increased SFG activation can be associated with faster reaction times found in the alerting cue condition in our experimental group, which, once again, corroborates the relevance of these regions in the context of visuospatial attention, thereby indicating that our mindfulness training had positive effects on attention on the behavioural level reflected in specific activation increases on the neuronal level.

Finally, there was an interesting significant negative correlation observed between PSS scores and activation of the right hippocampus after the mindfulness intervention. The hippocampus is a key brain area responsible for spatial attention and spatial mapping (L. Nadel, 2008), with the dorsal hippocampus playing an important role in cognitive functions and the ventral part modulating the behavioural adaptation to stress (Fanselow & Dong, 2010). Previous works have shown that there is a deactivation of the limbic system (i.e., hippocampus, hypothalamus, medio orbitofrontal cortex, and ACC) during psychosocial stress, triggered by a significant increase of cortisol (Pruessner et al., 2008). And later, it was also shown that this response is different in stress-responders (people with increase cortisol segregation during stressful situations) than in stress-non-responders (people with decrease cortisol levels during stressful situations) (Khalili-Mahani et al., 2010). In my experimental sample, I did see that the mechanism of more activation of the hippocampus was in line with lower PSS scores after the intervention, implying that after the mindfulness training an increased hippocampus activation is closely related to a decreased stress level, also in such a non-daily and rather stressful situation of an MRI experiment.

Other mindfulness studies on the hippocampus have shown functional and structural changes upon engaging in mindfulness meditation (Gotink et al., 2016; Hölzel et al., 2011; Sevinc et al., 2020, 2019). Sevinc et al. (2019) even reported that functional changes in the hippocampus correlated with trait-anxiety; a finding that was also seen in our experimental group (see Figure 4.16) and not surprising as stress and anxiety are closely related. Additionally, a study investigating structural changes in meditation practitioners found that the FA of white matter tracts surrounding the dorsal part of the hippocampus increased in meditators compared to non-meditators (Laneri et al., 2015). Similarly, another study using diffusion tensor imaging and probabilistic tractography detected a significant increase in FA in the UNC following mindfulness training and thus in a biger tract connecting, amongst others, the hippocampus with frontal regions (Hölzel et al., 2016). I was able to reproduce this finding in my study (see Figure 4.9). Moreover, voxel-based morphometry investigations on mindfulness meditation practitioners vs non-practitioners have shown greater gray matter concentration in the right hippocampus of meditators (Hölzel et al., 2008). Our results portraying increased meditation training-related activations in the right hippocampus and increased FA in the right UNC, together with earlier findings demonstrating significant structural effects of mindfulness training on the hippocampus suggest that, apart from the PCC, the hippocampus also represents a brain region which is susceptible to meditation and which, most probably, works according to the principle "form follows function" (i.e., increases in medium- or long-term activation lead to alterations in grey and white matter structure).

The UNC is a major association white matter pathway of the limbic system with afferent and efferent fibers (i.e., biderectionality) with a ventral part connecting the amygdala and hippocampal gyrus with the orbital cortex, and a dorsal section connecting the temporal pole cortex with the rostral end of the middle frontal gyrus (Wycoco et al., 2013; Kier et al., 2004). There are some DTI studies that argue that there is no concrete evidence that the UNC connects the hippocampus to frontal areas of the brain (Von Der Heide et al., 2013); however, based on post-mortum studies there is evidence that the UNC do connect the hippocampal gyrus with the pre-frontal cortex (Kier et al., 2004). Another important characteristic of the UNC is that it continues to develop in adults older than 30 years old, reaching its developmental peak at the age of 35 (Lebel et al., 2008, 2012). This large time span in its development makes the UNC fasciculus a pathway more prompt to FA changes driven by mindfulness trainings. The right UNC has also been strongly linked to emotional empathy, and abnormalities in its development have been seen in patients with psychiatric illnesess (Oishi et al., 2015; Von Der Heide et al., 2013); therefore, mindfulness meditation trainings can also be used as a mean to decreased the risk of developing psychiatric illnesses in young populations as seen in mindfulness interventions that helped protect mental health during the COVID-19 pandemic (Zhu et al., 2021; Sun et al., 2021; Antonova et al., 2021).

Our correlation analyses on DTI images between FA in the right UNC, psychological outcomes, and ANT RT could not revealed that these changes in white matter microstructure (i.e, increased WM integrity) might underlie the increased training-related activation within the hippocampus and PFC in association with attention. However, the role that the right UNC plays on emotional process such as empathy might explain why I saw increased changes in FA in the right UNC of our experimental group as previous studies have already reported an important correlation between mindulness meditation practice and increased empathy (Luberto et al., 2018).

5.3 ACC Activation/CBF Changes and Its Relationship With Stress

A recent review of 49 neuroimaging studies published between 2000 and 2020 on the effects of mindfulness and meditation on the CC in the healthy brain reported significant effects specifically on the ACC in 55% of these studies (Zsadanyi et al., 2021). Kwak et al. (2019) was able to demonstrate that after a four-day intensive Templestay meditation training naïve meditators showed increased activity in the ACC while performing the executive condition of the ANT; however, this finding contradicts a previous study where Kozasa et al. (2018) reported a reduced ACC activation on naîve meditators after a mindfulness training while performing a SWCT. In this study, naïve meditators showed a reduced ACC activation during the incongruent condition (i.e., during an executive attention task) of the SWCT after a seven-day Zen intensive meditation retreat, whereas the experienced meditators showed an increased ACC activation. At resting state, Tang et al. (2015) reported an increased CBF in the subgenual/adjacent ventral ACC in young (age $= 23 \pm 2$ years) naîve meditators after a five-day (30-min per day) IBMT training. In contrast, our CBF analysis at resting state showed a significant CBF decreased in the ACC of the experimental group (age $= 33 \pm 8$ years) after our 31 day (15-min per day) web-based mindfulness training. While it is difficult to conclude if mindfulness training increases or decreases ACC activation/CBF, a change in the ACC function after a short mindfulness training can reliable be reported.

This study furthermore investigated the role of cerebral perfusion in changes in perceived stress after our web-based mindfulness training. It is known that stressful events trigger increases in CBF (Bryan, 1990). Participants undergoing MRI scans, given the characteristics of the setting and noisy environment, are unfortunately exposed to a stressful situation. In our study, results of the pCASL imaging at resting state showed a significant decreased CBF in the ACC cortex of participants in the experimental group as a consequence of the mindfulness training. And, when I had a closer look at the correlation between CBF changes in the ACC and perceived stress changes in both the experimental and control group, I found a positive significant correlation in the control group not seen in the experimental group. This result or lack of correlation between perceived stress and the ACC CBF values in the experimental group might indicate that after the mindfulness training participants showed a less reactive response towards stress in this area of the brain. Previous studies have already shown that the ACC plays an important role in regulating cardiovascular reactivity to behavioural stressors (Critchley et al., 2003; Gianaros et al., 2004). And, a follow up study already linked the ACC to be involved more specifically in the regulation of blood pressure as a stressors-evoked response. (Gianaros et al., 2005). Moreover, a most recent study by the same group showed how this stress related reactivity in the ACC can lead to cardiovascular diseases (Gianaros & Wager, 2015). The reduced reactivity in the ACC to stressors shown in this thesis might be one mechanism of action on how mindfulness meditations trainings help in the treatment of cardiovascular diseases (Nardi et al., 2020). However, more research has to be done to show reproducibility of this finding, and therefore confirm this hypothesis. These results also showed the importance of incorporating CBF measurements in mindfulness studies to investigate and explore neurological pathways behind the positive impact of mindfulness meditation on well-being.

5.4 Limitations

In the current study, one limitation is the small sample size in the neuroimaging data. Finding participants that fit the requirements to undergo an MRI scan is not an easy task, 16 of our 72 recruited participants were not suitable for an MRI.

This is more than 20% of my main sample size. In addition, given the nature of longitudinal studies, I had an attrition rate of ∼10%. And, technical issues such as malfunction of the scanner or too much motion from the participants while being scanned reduced our sample size in another 15%. Therefore, I was able to include only 60% of the recruited participants in my final MRI sample (see Figure 3.1 for a more detailed overview of my sample size). Also, the non-normal distribution of my sample size regarding age range might have had some influence in the neuroplastic and CBF changes observed between the older and younger participants, which might have had affected the significance and effect sizes of my results. Future studies should take care in satisfying normal distributions of the sample size or used stratified analysis to determine effects of age on mindfulness trainings, as some previous studies have already reported different results among these groups (Shook et al., 2017; Mahlo & Windsor, 2021).

Anoter limitation was the inability to proof the compliance of participants with the respective training; this might have had and impact in the quality of our study, and therefore decreased the effect size of our results. Nonetheless, this study contributed to our understanding of mindfulness meditation neural mechanisms of action, its impact on pyschological outcomes, and improvements in cognition (i.e., attention). Future studies should incorporate online tracking functionalites or control questions within the training to assure training compliance of participants.

Unfortunately regarding our MRI acquisition, no cardiac or respiratoriy gating was used to remove pulsation/motion artifacts, or physiological noise. While this gating might not be that relevant for structural measurements, it is indeed strongly adviced in the acqusition of fMRI data to reduce noise sources; however, its implementation is challenging (Bulte & Wartolowska, 2017).

In our behavioural analysis, the differences in our baseline samples measuring trait anxiety and flow experience were not considered in the ANOVA analysis which could have introduced random differences between groups. A future approach to correct for this bias should incorporate the use of baseline scores as a covariate in the model, i.e., running an ANCOVA instead of an ANOVA. Moreover, the use of a passive control group should be considered as the active training in this study might have had some infulence on the psychological outcomes such as stress and well-being that might have overshadowed the effect of the mindfulness intervention.

Finally, our CBF analysis was based on absolute CBF values which does not account for CBF changes caused by caffeine intake, time of day when the measurement was taken or other unknown factors that might have affected CBF values. To eliminate the previous bias and corroborate the findings presented at this work, the same analysis should be run on relative CBF, i.e., by normalizing CBF values to another brain structure or to the global CBF value. And, to have a better understanding of the CBF changes induced by mindfulness practice, shorter and longer mindfulness interventions within the context of longitudinal studies with control groups (i.e., passive and active) should be explored.

5.5 Conclusions and Outlook

Our results indicate that a web-based mindfulness training has the potential to alter state of mind (i.e., mindfulness, flow experience, anxiety, and perceived stress level), cognitive performance (i.e., attention mechanisms), and underlying brain correlates (i.e., CBF and FA). Specifically, the brain of the experimental group showed greater activation in the SFG, PCC, and right hippocampus during the alerting condition of the attention network task, increased FA in the right UNC, and decreased CBF in the ACC at resting state.

My study showed that an intensive, standardized, short mindfulness training alters the CBF baseline of brain structures susceptible to meditation such as the ACC and Thalamus. CBF reductions in the ACC presumably indicated a less reactive response to stress after a mindfulness training. Also in this study, I showed that the decreased in stress in our experimental group is a precursor of improved brain function, more specifically by improving alerting attention. And finally, this increased in functionality might have reflected changes in white matter tracts connecting the underlying brain regions. However, more research has to be done to investigate the effects of the right UNC on attention, as the current study was unable to detect a significant correlation between the right UNC FA values and the ANT scores.

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

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List of Publications

Publications derived from this thesis

- Mora Álvarez M.G., Hölzel B.K., Bremer B., Wilhelm M., Hell E., Tavacıoğlu E. E., Torske A., and Koch, K. (2022). **Effects of a Web-Based Mindfulness Training on psychological outcomes, attention, and brain activation.** *Submitted to Mindfulness Journal*

Publications, which are not part of this thesis

- Bremer B., Wu Q., Mora Álvarez M.G., Hölzel B.K., Wilhelm M., Hell E., Tavacıoğlu E. E., Torske A., and Koch, K. (2022). **Mindfulness meditation increases default mode, salience, and central executive network connectivity.** Scientific reports, 12(1), 13219. doi: 10.1038/s41598-022-17325-6

Poster presentations derived from this thesis

- Mora Álvarez M.G., Bremer B., Hell E., Hölzel B.K., and Koch, K. **Increased Cingulate Cortex Activation in the Alerting Network of Attention after a 31 Days Web-based Mindfulness Training.** *12th FENS Forum of Neuroscience (July 2020).*

- Mora Álvarez M.G., Dorosti N., Hölzel B.K., Bremer B., Hell E., Tavacıoğlu E. E., and Koch, K. **Effects of a Web-Based Mindfulness Training on Cerebral Blood Flow** *Annual meeting Organization for Human Brain Mapping (OHBM) (June 2022).*

- Mora Álvarez M.G., Hölzel B.K., Bremer B., Hell E., Tavacıoğlu E. E., and Koch, K. **Increased Fractional Anisotropy (FA) in the Left Anterior Corona Radiata and Right Uncinate Fasciculus After a 31-Day Web-based Mindfulness Training** *13th FENS Forum of Neuroscience (July 2022).*

Appendix A

A.1 Mindfulness Training

Table A.1 shows the structure and content of the mindfulness meditation training.

A.2 Health-Enhancement Program

Table A.2 shows the structure and content of the health-enhancement program.

Table A.1: This is the structure and content of the mindfulness meditation training.

Session	Format	Theory	Practice
1	Video	Introduction to Mindfulness	Mindful Breathing A
2	Audio	NA	Mindful Breathing A
3	Audio	NA	Mindful Breathing A
4	Video	Arriving in Presence	Mindful Breathing B
5	Audio	NA	Mindful Breathing B
6	Audio	NA	Mindful Breathing B
7	Video	Arriving in the Body	Bodyscan A
8	Audio	NA	Walking Meditation
9	Audio	NA	Bodyscan A
10	Video	Subjectivity of Perception	Bodyscan B
11	Audio	NA	Walking Meditation
12	Audio	NA	Bodyscan B
13	Video	Comunicating Mindfully	Mindful Attention to Body Sensations
14	Audio	NA	Mindful Attention to Body Sensations
15	Audio	NA	Mindful Attention to Body Sensations
16	Video	Non-judgement	Mindful Attention to Body Sensations
17	Audio	NA	Mindful Listening
18	Audio	NA	Mindful Listening
19	Video	Dealing with Stress	Mindfully Approaching Emotions
20	Audio	NA	Mindfully Approaching Emotions
21	Audio	NA	Mindfully Approaching Emotions
22	Video	Turning Towards instead of Turning Away	Turning Towards instead of Turning Away
23	Audio	NA	Approaching Unpleasant Feelings
24	Audio	NA	Awareness of Thinking
25	Video	Positive Qualities	Loving Kindness
26	Audio	NA	Loving Kindness
27	Audio	NA	Loving Kindness
28	Video	Decentring	Open Monitoring
29	Audio	NA	Open Monitoring
30	Audio	NA	Silent Meditation
31	Video	Reflecting the course	Silent Meditation

NA: not applicable

Table A.2: This is the structure and content of the health-enhancement program.

Session	Format	Theory
1	Video	Sleep
2	Audio	Chronic Pain
3	Audio	Light Exposition and Health
4	Video	Sleep Disturbances
5	Audio	Body Memory
6	Audio	Migraine
7	Video	Burnout
8	Audio	Nutritional Supplements
9	Audio	Social Inequality and Health
10	Video	Sore Muscles/Vegan Diet
11	Audio	Time Perception
12	Audio	Gender Specific Health Experience
13	Video	Vitamins
14	Audio	Health Impacts of Dieting
15	Audio	Aging
16	Video	Sugar
17	Audio	Maintaining a Diet
18	Audio	Self-Deceit
19	Video	Raw Foods
20	Audio	Migration and health
21	Audio	Epigenetics
22	Video	Sensible Footwear
23	Audio	Obsessive-Compulsive Disorder
24	Audio	Self-Efficacy
25	Video	Busting Breakfast Myths
26	Audio	Cardiovascular
27	Audio	Hypnotherapy
28	Video	Staying Active in the Office
29	Audio	Negative Empathy
30	Audio	Pain Perception
31	Video	Physical Activity