Real-time fMRI Neurofeedback and Smartphone-based Interventions to Modulate Mental Functions

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by

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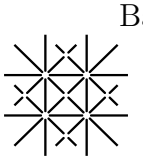

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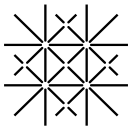

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Contributions to individual publications

This cumulative thesis contains the four publications listed below, all of which have been the joint effort of several contributors. The numbers given with the references indicate my contributions to each of the publications. To do this, I follow the *CRediT Taxonomy*, a system created to determine and credit individual author contributions which was adopted by several major scientific publishers (see `http://casrai.org/credit` for details). It offers the following 14 contributor roles:

1 Conceptualization — **2** Data Curation — **3** Formal Analysis — **4** Funding Acquisition — **5** Investigation — **6** Methodology — **7** Project Administration — **8** Resources — **9** Software — **10** Supervision — **11** Validation — **12** Visualization — **13** Writing – Original Draft Preparation — **14** Writing – Review & Editing

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Abstract

Our brains are constantly changing on a molecular level depending on the demands thrown at them by our environments, behavior, and thoughts. This neuronal plasticity allows us to voluntarily influence mental functions. Taking conscious control over mental functions goes potentially back millenia, but it was psychotherapy since the early 20th century which moulded this concept into a concrete form to target specific mental disorders.

Mental disorders constitute a large burden on modern societies. Stress-related disorders like anxiety and depression particularly make up a large part of this burden and new ways to treat or prevent them are highly desirable, since traditional approaches are not equally helpful to every person affected. This might be because the infrastructure is not available where the person lives, their schedules and obligations or financial means do not enable them to seek help or they simply do not respond to traditional forms of treatment.

Technological advances bring forth new potential approaches to modulate mental functions and allow using additional information to tailor an intervention better to an individual patient. The focus of this dissertation lies on two promising approaches to cognitively intervene and modulate mental functions: real-time functional magnetic resonance imaging neurofeedback (rtfMRInf) on one hand and smartphone-based interventions (SBIs) on the other. To investigate various aspects of both these methods in the context of stress and in relation to personalized interventions, we designed and conducted two experiments with a main rtfMRInf intervention, and also with ambulatory training of mental strategies, which participants accessed on their mobile phones.

The four publication this thesis entails, are related to this topic as follows: The first publication focuses on rtfMRInf effects on the physiological stress response, exploring whether neurofeedback could reduce stress-related changes in brain activity and blood pressure. The second publication focuses on rtfMRInf effects on psychological measures related to the stress response, namely on arousal and mood, based on data from self-report by the participants. The third publication focuses on rtfMRInf methodology itself, looking at complex connectivity data between major neural networks. Finally, the fourth publication focuses on personalized prediction of intervention success of an SBI using data from previous training days.

Contents

List of Abbreviations

ACC	Anterior cingulate cortex
BOLD	Blood-oxygen-level dependent
CBT	Cognitive behavioral therapy
CEN	Central executive network
DALY	Disability-adjusted life year
DMN	Default-mode network
EDA	Electrodermal activity
EEG	Electroencephalography
eHealth	Electronic health
EMG	Electromyography
fMRI	Functional magnetic resonance imaging
GAD	Generalized anxiety disorder
HRV	Heart rate variability
ICBT	Internet-based cognitive behavioral therapy
ICT	Information and communication technologies
IC	Insular cortex
MBSR	Mindfulness-based stress reduction
mHealth	Mobile health
MRI	Magnetic resonance imaging
PD	Panic disorder
PTSD	Post-traumatic stress disorder
RCT	Randomized controlled trial
rtfMRInf	Real-time functional magnetic resonance imaging neurofeedback
SBIs	Smartphone-based interventions

SN	Salience network
TMS	Transcranial magnetic stimulation
WHO	World Health Organization

1 Introduction

1.1 Change and the brain

Life is change. With every thought we think, with every move we make, our brain changes on the molecular level. And when our brain changes, our world changes, for our world is essentially what our brain makes it to be [Frith, 2007, Hohwy, 2016].

In 1949, Donald O. Hebb published his seminal book "The Organization of Behavior: A Neuropsychological Theory" that would shape our understanding of core cognitive processes and their biological basis for decades. He proposed that repeated activation of individual neuronal cells, in unison, changes the physical structure of the connection between these cells and consequently changes what our brain is capable of, its underlying mental functions and processes – often summarized since as *"neurons that fire together, wire together"* and dubbed *Hebb's rule* or *Hebbian Theory* [Hebb, 1949]. This is the basic process behind learning and memory.

Some 20 years later, researchers began to report evidence for the proposed link between repeated activation and neuronal connection [e.g. Bliss and Lomo, 1973]. Kandel and colleagues later described additional supporting findings on the molecular level, after investigating the large neurons in the *Aplysia* or sea hare – a species of sea slugs [for reviews see Kandel et al., 2009, Mayford et al., 2012]. Later they further investigated the interplay between molecular memory processes and genes [Kandel, 2001].

Taken together, this research lay the scientific foundation for the phenomenon called *neur(on)al plasticity*, or *neuroplasticity*, the idea that our brains are changeable and that they remain so throughout our lives. More precise definitions in an encyclopedia of neuroscience and a book on neurostimulation describe it as *"The capacity of neuronal systems (...) for change of anatomical and functional features"* [Binder et al., 2009] and *"Reorganization of the brain's structure and function in response to intrinsic or environmental challenges."* [Stagg, 2014, p. 146], respectively.

And such changes do not have to take years of practice. In fact, the brain can be rather quick in adapting to behavioral or environmental demands under certain circumstances. A memorable demonstration of this was described by Draganski et al. [2004]. They reported that in people who learned to juggle, structural changes in the cortex were visible after only three months of training. Classen et al. [1998] showed that effects of plasticity are even measurable after only 30 minutes of training. Their participants were able to change the direction of thumb movements evoked by transcranial

magnetic stimulation (TMS), by deliberately training other thumb movements. These effects persisted for only 15-20 minutes and were thus reversed again as quickly as they had come into existence. Still, it shows how quickly our brain can start to change depending on our behavior.

Another groundbreaking discovery of recent decades in regard to the changing brain, is that the adult brain is not just able to rewire neurons differently throughout the whole life span, but also to create completely new neurons (*neurogenesis*) — a process long thought to be exclusive to early developmental stages [Eriksson et al., 1998, Ernst et al., 2014].

Why is neural plasticity central to this thesis? Because modulating a mental function, modulating anything our brain does by learning and practicing (mentally or physically), is impossible without it. But this phenomenon does not just support us in our everyday learning and use of our mental capacities, it also comes into play when we want to change something that does not work as desired, when we struggle with mental difficulties or even disorders: Psychotherapy makes use of plasticity, as is the underlying assumption in the book by Cozolino [2017], who writes that if therapy has any effect on the symptoms of a mental disorder, it is fair to assume that the patient's brain changed [Cozolino, 2017, p. 14]. Pascual-Leone et al. [2005] go as far to describe plasticity as inseparable from any neural activity, explicitly including mental practice. In their view, the essential question is to figure out how to leverage this phenomenon: *"The challenge we face is to learn enough about the mechanisms of plasticity to modulate them to achieve the best behavioral outcome for a given subject."* [Pascual-Leone et al., 2005, p. 377]

1.2 Modulation of mental functions

The term *mental function* (or cognitive function) was described as something produced by a given structure within a species, which is reproducible and inheritable and which exists due to some evolutionary adaptive value to the species [Proust, 2009]. Hence, a mental function is linked to an underlying structure, for example a specific region of the brain, and has an evolutionary adaptive value, i.e. serves an evolutionary purpose.

The idea to volitionally take control over or modulate mental functions, and thus make use of the neuronal plasticity as described above, goes back millenia, though it was not described as such — in terms of changing specific brain activity — considering the state of knowledge on biological processes back then. Just imagine a monk living in the 4th century BC somewhere in the area of today's India. Without getting into any details on the philosophy underlying Buddhism, let us consider what practitioners in this and similar traditions have been doing for thousands of years: they used their mind to influence their bodies, and consequently to influence their world, which is constantly being built by our mind's interpretation of what it perceives from our surroundings and inner

workings through sensory input [Frith, 2007, Hohwy, 2016].

Over the last decades, science has begun to unravel what practitioners of meditation have been doing for millennia, and what the underlying biological processes are [Tang et al., 2015]. It is hardly surprising then, that meditative practices rooted in such traditions, sometimes explicitly stripped of their spiritual and religious underpinnings, are increasingly reported to support mental and physical health [for reviews see Grossman et al., 2004, Arias et al., 2006], are gaining traction as treatments, and make their way into medical and psychotherapists' practices. One example is the Mindfulness-Based Stress Reduction (MBSR) program, introduced and spread in western countries by molecular biologist Jon Kabat-Zinn [Kabat-Zinn, 2013].

In regard to changing the brain itself and neural plasticity, changes in diverse structural (e.g. cortical thickness, grey-matter volume and density) and functional characteristics have been observed in practitioners of various meditation techniques [Tang et al., 2015, Wheeler et al., 2017]. For example, Lazar et al. [2005] reported increased thickness in several cortical regions when in people who had been practising insight meditation regularly for several years, for multiple hours each week. Farb et al. [2013] found changes in the insular cortex (IC) activity related to attention in MBSR practitioners who conducted a standard 8-week course compared to control participants on a waiting list.

Besides techniques based on ancient meditative practices, there are other approaches which are applied today to introduce fundamental changes in our brains and through that to improve our mental and physical health. Psychotherapy, as it developed over the course of the last century, stands out as a collection of different cognitive and behavioral methods within different schools which are used to induce such changes [Cozolino, 2017]. Physical exercise has also been found to lead to structural and functional changes [Ferris et al., 2007, Erickson et al., 2011], as has practicing something repeatedly (voluntarily or not): In taxi drivers in London, for example, researchers found regions involved with spatial long-term memory (areas in the hippocampus) to be larger than in control participants and the volumes of these regions were correlated with seniority of the drivers — indicating improved spatial memory capacity in these people and changes to the brain to account for this specific environmental demand [Maguire et al., 2000].

In the publications of this thesis, we looked at the modulation of a mental function highly relevant for mental health (the stress response) using short mental interventions in combination with specific methods in the context of personalized interventions. The mental interventions we used are linked to both mindfulness meditation and psychotherapy.

1.3 Stress

1.3.1 Stress-related mental health burden

Stress is a major burden of modern society; one that seems inevitable to avoid in our daily lives. Increasing financial costs can be attributed to it, directly by health-care costs or indirectly for example via absenteeism of people who developed stress-related disorders [European Commission, 2000, APA Working Group on Stress and Health Disparities, 2017]. Depressive and anxiety disorders, the main stress-related mental disorder groups, are the largest contributors to disability-adjusted life years (DALYs) among mental and substance use disorders, accounting for 40.5% and 14.6% of DALYs related to mental and substance use disorders, respectively [Whiteford et al., 2013].

The rise of technology seems to increase this problem by exposing us to more information than ever before and enabling immediate non-stop global communication [Tarafdar et al., 2007, Ayyagari et al., 2011], but there's a chance technology might actually help to deal with this problem. Delivering treatments to patients via mobile devices is an example of a potential helpful application of mobile gadgets to counter stress-related problems. Thus it is also part of the interventions we applied in our experiments behind the publications included in this thesis.

1.3.2 The stress response as target of modulation

In our experiments, we chose the stress response as target for our interventions to modulate a mental function. The human stress response is a complex cascade of events in our body following the confrontation with an internal or external stressor, which can basically be anything perceived as a threat. It encompasses psychological, physiological, and behavioral aspects and is orchestrated by the release of various hormones, which make up the endocrine part of this system. The essential biological structures that make up the stress system are the hypothalamus, the pituitary gland and adrenal glands, dubbed the hypothalamic–pituitary–adrenal (HPA) axis. The fundamental *fight-or-flight response* to stress, described by Walter Cannon already in 1932 [Cannon, 1932, Fink, 2017], can be summarized as follows: In a first quick response to a stressor, the hypothalamus activates the sympathethic nervous system directly via release of adrenaline by the adrenal glands, activating the body for action (e.g. increased heart rate, blood pressure, breathing, blood flow to muscles and vital organs, release of glucose for energy support). A second, slower response releases glucocorticoids from the adrenal glands, following a cascade of releasing hormones along the HPA axis [Cullinan, 2009, de Kloet et al., 2005].

But not every demand on us triggers a full fight-or-flight response and neither would every demand be interpreted equally as a stressor. In fact, the potential human response to a stressor is more like a toolbox rather than an ON/OFF-switch. Other types of responses

that can be activated by a stressor under certain circumstances have been discovered more recently, most notably the *tend-and-befriend response* [Taylor et al., 2000, Taylor, 2006, Taylor and Master, 2011] in which oxytocine plays a key role, and the *challenge response* which resembles the *flow state* [Nakamura and Csikszentmihalyi, 2014] and depends on whether a demand is perceived as a threat or challenge to us, in regard to our own assessment of our coping abilities [Jamieson et al., 2012]. Our perception of the stressor and mindset about how stress effects us and how we can cope with it has an influence on which response type is triggered by an individual stressor [McGonigal, 2015]. This is already evident in Lazarus and Folkman's definition of psychological stress: "a relationship with the environment that the person appraises as significant for his or her well-being and in which the demands tax or exceed available coping resources."[Lazarus and Folkman, 1986, p. 63]

The whole array of stress responses are essential to survival, which is why they developed and remained part of our experience throughout the evolutionary history. However, chronic stress and repeated activation of the full fight-or-flight response can be harmful [de Kloet et al., 2005]. This might partly be caused by a misinterpretation of stressors and their relevance, which can trigger a full fight-or-flight response at times when it is not necessary to our survival. Besides being linked to mental disorders, chronic stress has also been associated with physical issues like hypertension [Sparrenberger et al., 2009]. Acute stressors and chronic stress seems to even hinder neurogenesis in the adult hippocampus, at least across different rodent species and in marmosets [Mirescu and Gould, 2006, Snyder et al., 2011, Schoenfeld and Gould, 2012].

But our stress response is not unchangeable, loaded upon us by birth, never to be budged. Fortunately, we have a say in how we react to a given stressor. Just in recent years it has been found that even short and seemingly simple interventions focusing on people's mindset towards stress and what it does with us, can have lasting effects on how stress actually effects us [McGonigal, 2015]. Given this mendability of the stress response, the large burden presented by stress-related health issues and the lack of research about using neurofeedback in the context of stress, we decided to target the stress response with our interventions.

1.4 Personalized interventions

The idea of personalized treatments or interventions has become a promising field in medicine generally (under the terms *personalized* or *precision medicine*) [Collins and Varmus, 2015], but also in the treatment of mental disorders in particular [Insel and Cuthbert, 2015]. In medicine, personalization is mostly related to tailoring drug treatments to a patient based on genetic markers [e.g. Katsanis et al., 2008, Hamburg and Collins, 2010]. This approach was suggested for psychotherapy as well [Beevers and McGeary, 2012], but there is other data based on which psychotherapeutic interventions

can be fitted to a patient. The basic idea of using personal data for this purpose in psychotherapy is not new: Paul [1967] already suggested that outcome research should be guided on the principle of finding the specific treatment for each individual, problem, and circumstances. With the help of new technology we get easier access to more such data, be that biological or behavioral.

In the following, I will present two rather different approaches which can be regarded as part of the development in direction of more personalized interventions, namely neurofeedback and smartphone-based interventions (SBIs). Neurofeedback uses signals directly recorded from brain activity, while SBIs can make use of various behavioral data recorded via the smartphone to fit and adapt interventions to a given patient.

1.5 Neurofeedback

Recording human brain activity through medical imaging has inarguably propelled medicine and human neuroscience over the last decades, as evidenced by the Nobel Prize in Physiology or Medicine of 2003 being awarded to two scientists pivotal to the development of magnetic resonance imaging [MRI; Nobel Media AB, 2003]. But let us move one step ahead and imagine you could watch and consciously modulate your brain's activity in action. Instead of appearing at the scene after the action and trying to figure out what happened, you are right there and can actively observe and take part in what your brain does while it does it. Advances in the technology behind functional MRI (fMRI) and data analysis, which emerged in the early 2000s, allow exactly that and guided the path for astonishing new insights and applications. While in the brain scanner, participants can get visual feedback of the activity in a specific region of their brain and consciously train to change it.

Neurofeedback describes any procedure to record signals of brain activity, process this data, and return them to the individual in a comprehensible form in real-time or near real-time. *Neurofeedback training* adds the idea that individuals can then use this signal, to consciously modulate the brain activity which generated it [e.g. Sitaram et al., 2017]. The concept of neurofeedback branched off the more general term *biofeedback*, which includes the use of any biological signal measured and fed back for the purpose of an intervention. Biofeedback was already applied for the treatment of various mental disorders including anxiety disorders (phobias, generalized anxiety disorder [GAD], post-traumatic stress disorder [PTSD] and panic disorder [PD]), depression, and Schizophrenia, using peripheral psychophysiological measures like respiration, blood pressure, heart rate, heart rate variability (HRV), electrodermal activity (EDA), or facial electromyography (EMG)[for a review see Schoenberg and David, 2014].

The history of neurofeedback goes back over 40 years[Lubar and Shouse, 1976] and has long been restricted to recordings with electroencephalography (EEG). EEG

neurofeedback has been successfully applied in a range of disorders, most notably in anxiety disorders [Moore, 2000, Hammond, 2005, Schoenberg and David, 2014], and the behavior disorder attention deficit hyperactivity disorder (ADHD)[Arns et al., 2009].

The development of real-time MRI, which is now routinely used in guiding neurosurgery [Kesavadas et al., 2007, Möller et al., 2005], lay the foundation for feedback paradigms in fMRI experiments. Early rtfMRInf experiments had quite a long delay between signal creation in the brain and feedback display, due to data processing time and the biological temporal limit of the blood-oxygen-level dependent (BOLD) signal. Yoo and Jolesz [2002] for example had a delay of approximately 60 s in their first report on fMRI-based neurofeedback, as did Posse et al. [2003]. As the method became more feasible using fMRI and these delays could be shortened, several new applications for the technique and the use of it in regard to mental disorders were proposed and experimentally tested [Weiskopf et al., 2007, Weiskopf, 2012, Stoeckel et al., 2014]. A good overview over the development of the approach and the conducted experiments is available from recent reviews by Sitaram et al. [2017] and Thibault et al. [2018]. The main advantage of fMRI-based neurofeedback in comparison to that based on EEG signals, is the increased spatial resolution which allows targeting brain areas much more precisely and also the fact that one can target areas located more deeply within the brain, such as regions related to emotion processing or memory, which becomes increasingly important when considering clinical applications of the method [Weiskopf, 2012].

1.6 Smartphone-based interventions

Smartphone-based interventions (SBIs), or, in a broader sense *mobile interventions* with any portable electronic device, offer a new tool to bring people in contact with psychoeducational information, psychotherapeutic practices, or any other techniques that might help them deal with mental disorders. Such interventions can be categorized under the term *mobile health (mHealth)* or even broader under *electronic health (eHealth)*, which comprise the use of mobile devices and any information and communication technologies (ICT) in health care, respectively [World Health Organization, 2011]. The ubiquity of mobile communication devices, the wealth of data which can be gathered by them via internal or additional sensors, and the customizability of interactive applications, predestine them as a means to deliver personalized mental health interventions.

Adding mobile technology to the treatment of mental disorders allows to reach more people, especially those who might otherwise get no treatment at all. There might be various reasons for this: sheer lack of available therapists, lack of money, lack of a health care system that allows the patients to see a therapist, or avoidance by client (e.g. in social anxiety and other disorders with low treatment-seeking behavior due to the disorder itself). Arnberg et al. [2014] already pointed out in a review on psychological online interventions, that almost 40% of the population will sooner or later need treatment for a

depressive or anxiety disorder [Wittchen et al., 2011]; covering all these potential patients is a challenge that needs innovative interventions beyond traditional face-to-face therapy if we want to avoid a situation where large proportions remain untreated. Even in developed countries up to 50% might otherwise not receive any treatment; in developing countries it might be up to 85% [Demyttenaere et al., 2004].

But even when treatment is available, not everyone takes advantage of it. For example, just about one third of people with an anxiety disorder in a large US survey perceived the need to seek professional help and only about a quarter finally does seek such help [Mojtabai et al., 2002]. People with social anxiety might be even less likely to seek help from a medical professional, due to the likely perception that their illness is due to personal weakness [Coles and Coleman, 2010], and because the main symptomatology of the disorder makes them generally less likely to approach an unknown person (like a therapist) in seek for help. Mobile technology can thus help to lower the threshold to seek mental health treatment, especially in disorders where avoidance of face-to-face meetings is part of the disorder's symptomatology itself (e.g. social anxiety).

Another advantage of SBIs is that mobile devices are available around the clock and due to that one can also use the help of professional interventions outside of office hours of a therapist. Micro-interventions, lasting only a few minutes can fit in busy daily schedules of people who would otherwise be unable to adhere to a fixed schedule of appointments with a therapist lasting an hour or more.

1.6.1 Leapfrogging face-to-face therapy

It might seem counter-intuitive to suggest helping people in developing countries or remote regions with mental health interventions via mobile technology. But let us consider that the introduction of mobile phones has in some regions allowed people global communication where they never had access to landline phones. This jump over a technological step was named *telecom leapfrogging* [e.g. Huang, 2011, Donner, 2008]. Just as it did with telecommunication, mobile technology might allow people in such regions to jump from not having any access to professional mental health support, to using mobile technology to get such support, without every having implemented an infrastructure for traditional face-to-face therapy. In other places it might simply be one next developmental step, one way to supplement the already existing mental health care infrastructure.

1.6.2 Therapy without therapist?

The question arises, whether therapy without a therapist, that is without direct face-to-face contact or with only minimal contact can help at all. This would be a necessary basis for any interventions purely accessed via mobile technology. For anxiety disorders and mood disorders there is already supporting evidence suggesting that not

only minimal-contact therapies, but also pure self-help — without any face-to-face contact with a mental health professional — can be rather effective if the patients are sufficiently motivated [for reviews see Newman M.G., Szkodny L.E., Llera S.J., 2011, Arnberg et al., 2014], even when directly compared to face-to-face therapy [Carlbring et al., 2018, Cuijpers et al., 2010].

Handing patients tools and then letting them apply these is not new to psychotherapy. In a face-to-face therapy session of cognitive behavioral therapy (CBT), a therapist might just as well teach a certain exercise to a patient and then let them practice the exercise until they see each other again in the next session. We find another indicator that therapeutic practices without direct contact to a therapist works, in the results of research into the efficiency of self-help books or *bibliotherapy*. This form of treatment, also known as *self-administered treatment* (SAT) — basically only giving the tools without any therapeutic face-to-face interaction — has already been shown to help with various disorders [Watkins and Clum, 2007], including stress-related disorders like burnout [Hofer et al., 2018].

The next indicator comes from *online-therapy* (also *internet-based therapy* or *e-therapy*), where patients interact with purpose-built websites which guide them through treatments. This form of delivery of psychotherapeutic methods was investigated over the last decades, and shows potential to help with various anxiety disorders (e.g. social anxiety [Berger et al., 2009, Furmark et al., 2009, Carlbring et al., 2007], specific phobia [Vigerland et al., 2013], generalized anxiety disorder [Paxling et al., 2011, Titov et al., 2009]) and mood disorders [e.g. Mackinnon et al., 2008, Christensen et al., 2006]. And that not just with adult patients, but also with children and adolescents [Stasiak et al., 2016, Vigerland et al., 2013]. A recent review and meta-analysis of mindfulness-based online interventions showed that the found effects are similar to face-to-face therapy in the context of stress, but might be somewhat smaller than face-to-face therapy in case of interventions aimed at anxiety and depression [Spijkerman et al., 2016], while an earlier review had found comparable effects also in this case [Barak et al., 2008]. For internet-based cognitive-behavioral therapy (ICBT), a review by Arnberg et al. [2014] reported moderate short-term efficacy for mild and moderate depression, panic disorder, generalized anxiety disorder, and social anxiety. However, these effects were mostly in comparison to waiting list controls and not to face-to-face therapy, highlighting a need for trials with such comparisons.

But when a book will do, why even bother dealing with setting up a mobile application or website? Because these methods additionally allow to track progress and success of the intervention, which does not only help to improve treatments themselves, by informing their developers with what worked, but additionally allows to tailor the treatment to a person, who then optimally only receives those methods which work for them and also to a suitable time. Furthermore, such applications or websites can continuously gather

data throughout the course of an intervention (e.g. via behavioral logs or questionnaires) and potentially be combined with biofeedback or neurofeedback methods (see section 1.5). Especially mobile devices can supply a wealth of information: usage data from applications (e.g. how often, for how long, and at what time of the day a person interacts with an application), voice recording, measurement of biological information via additional sensors (e.g. cortisol levels, heart rate, blood pressure). They also have sufficient computational speed to allow predictive calculations like text or voice analyses, which become even more powerful in combination with other information.

1.7 Research questions

Focusing on these two approaches to modulate mental functions, rtfMRInf and SBIs, both of which enable personalizing interventions, we started with a broad research question, out of which two complex experiments emerged. We then used data from these experiments to answer the individual questions investigated in the four publications included in this thesis. The main research question underlying this thesis is: **Can rtfMRInf and SBIs be used to volitionally modulate mental functions, especially in regard to the stress response?** We designed and conducted two experiments with rtfMRInf as main intervention and with additional smartphone-based training, which consisted of short interventions of mental strategies over several days, through which participants were guided by videos that they accessed on their mobile phones. The four publications included in this thesis are related to the main research question as follows:

- The first publication focuses on rtfMRInf effects on the physiological stress response, exploring whether neurofeedback could reduce stress-related changes in brain activity and blood pressure.
- The second publication focuses on rtfMRInf effects on psychological measures related to the stress response, namely on arousal and mood, based on questionnaire data from self-reports.
- The third publication focuses on rtfMRInf in connection with mindfulness, investigating whether the functional connectivity between two major brain networks, mediated by a third network, are associated with levels of mindfulness and whether neurofeedback training could increase this association.
- The fourth publication focuses on one aspect of SBI in regard to personalized interventions, namely whether data from earlier training days could predict intervention success on later training days.

2 Original research papers

2.1 Publication 1: Real-time fMRI neurofeedback to modulate the neural and cardiovascular stress response: A randomized controlled trial

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Real-time fMRI Neurofeedback to Modulate Neural and Cardiovascular Stress Response: A Randomized Controlled Trial

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Short Title: fMRI Neurofeedback and Stress

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Abstract

Background Stress-related disorders are leading causes of global disease burden. Innovative treatments are urgently needed. **Objective** Investigate whether real-time functional magnetic resonance imaging neurofeedback (rtfMRInf) can modulate neural and cardiovascular stress response. **Methods** Participants underwent rtfMRInf with experimental or sham control condition. We induced stress with the Stroop color-word interference task, giving participants in some trials specific ('fixed') and in others 'free-choice' of mental strategies for brain activity regulation. Primary outcomes were activation changes in anterior cingulate (ACC) and insular cortex (IC), and changes in blood pressure. **Results** Time series analyses revealed differences between conditions: Participants in the experimental (n=17) versus control (n=13) condition had i) lower ACC Stroop responses (beta=–0.03, 95%CI[–0.04,–0.01], t_{1009}=–4.16, p=3.29x10^{-5}) and ii) lower ACC (beta=–0.22, 95%CI[–0.26,–0.18], t_{7922}=–10.95, p=1.04x10^{-27}) and IC (beta=–0.27, 95%CI[–0.31,–0.23], t_{8955}=–13.42, p=1.08x10^{-40}) activity during free-choice compared to fixed-strategy trials. Blood pressure did not significantly differ between conditions. In the experimental condition, diastolic blood pressure was correlated i) over trials with IC Stroop responses (r=0.567, p=0.0220) and ii) regarding its individual differences between fixed-strategy and free-choice trials with IC (r=0.777, p=3.96x10^{-4}) and ACC activity (r=0.846, p=3.69x10^{-5}) **Conclusions** We provide first evidence that rtfMRInf allowed modulating brain activity in stress-related regions, especially using free-choice strategies. While it did not transfer to blood pressure reactivity, rtfMRInf was linked to coupling of learning effects in brain and cardiovascular stress responses, suggestive of rtfMRInf potentially enhancing peripheral outcomes of interventions targeting the brain. **Trial registration** ClinicalTrials.gov NCT01921088

1 Introduction

Psychosocial stress and stress-related disorders are increasingly burdening industrialized countries. Already in 2000, their annual cost in the European Union was estimated at 20 billion euros [1]. In 2014, 25% of European workers reported experiencing work-related stress most or all the time at work [2]. At the same time in the United States, 49% of surveyed people reported a major stressful event within the last year [3].

Stress affects both mental and physical health and can lead to dire consequences. High blood pressure is a likely culprit through which stress affects people's health negatively in the long term. Especially chronic psychosocial stress was identified as a potential cause for hypertension [4,5], which is globally the leading modifiable risk factor of mortality, and the majority of the affected population is not even aware of it [6,7]. Furthermore, treatment resistance (to common pharmacological treatment) is widespread – a Swedish study reported it at 17% [8]. This makes efforts to develop alternative interventions against stress urgent and important. Notably, models about the brain processes involved in psychosocial stress have been suggested [4], but current interventions in stress-reduction do not leverage this knowledge.

One approach to clinically translate neuroscientific findings is neurofeedback [9,10]. Neurofeedback enables people to intentionally modulate specific brain activity underlying behavior or experiences. In neurofeedback training, a trainee's own brain activity signal is fed back intelligibly to the subject to allow volitional control over the activity by observing and adjusting it in (near) real-time. Real-time fMRI-based neurofeedback (rtfMRInf) has been applied, for example, to reduce chronic pain [11], improve attention and reduce other symptoms of attention deficit hyperactivity disorder (ADHD) [12], lift mood [13,14], or foster anxiety regulation in specific phobia [15].

We investigated whether rtfMRInf training in combination with mental strategies could lower the neural and cardiovascular stress response induced by a cognitive task. Participants underwent the Stroop colour-word interference task (the Stroop), besides trying to decrease the effect of this stressor by using mental strategies. The Stroop has been shown to trigger central and peripheral stress-reactions, including blood pressure increase, heart rate and salivary cortisol reactivity [16]. The blood pressure reactivity to this and other cognitive tasks was also found to be predictive for carotid intima-media thickness, a known marker for atherosclerosis [17].

As main hypotheses of our study, we tested whether in the experimental vs. control condition, brain activity in target stress-related regions independent of a stressor were reduced. Based on established findings for neuronal correlates of stress responses in the Stroop task [16,18], we defined a set of anatomical regions of interest (ROIs) to use as the target regions for our neurofeedback training. These regions comprised the left and right anterior cingulate cortex (ACC) and insular cortex (IC) from the Automated Anatomical Labeling (AAL) ROI library [19]. We wanted to further explore, whether applying freely chosen differed from fixed mental strategies with regard to neurofeedback effects. Here, we wanted to test whether, i) brain activity responses to the Stroop task in target stress-related regions were reduced, and, ii) blood pressure responses to the Stroop task were reduced. Further, we examined the association between learning effects over time in brain and blood pressure reactivity in both conditions and assessed differences in adverse events between conditions. Since, even though rtfMRInf appears to be safe [20], its safety in the context of stress-reduction still awaits confirmation.

2 Materials and Methods

(For brevity, this section is kept to a minimum. A detailed methods section can be found in the Supplement of this publication. For details on aspects of the experiment not presented in this publication, see our earlier publications [21, 41])

2.1 Participants

We recruited participants at the Korea University via ads on the university website and a local bulletin board. We assessed the applicants eligibility based on these criteria: male, 18-65 years old, right-handedness, no color-blindness, no history of cardiovascular or neurological diseases or severe mental disorders, sufficient English language skills to follow the experimental instructions, and familiarity with smartphone-use to carry out the ambulatory training. Participants gave written informed consent and Korea University's institutional board approved the study protocol (approval number: KU-IRB-10-38-A-2(E-A-1)(E-A-1)(E-A-3)). Participants received 60 000 KRW (≈57 USD) in compensation.

2.2 Outline of study procedures

2.2.1 Overall study procedure

We conducted a block-randomised, single-blinded parallel-group neurofeedback study with sham-feedback control condition (registration: ClinicalTrials.gov NCT01921088), consisting of three laboratory visits and 13 days of ambulatory mental training. We screened applicants via telephone for any history of neurological or mental disorders and invited those suitable to a laboratory visit ("preliminary testing day") to assess their eligibility. Included applicants visited the laboratory twice (14 days apart) for the main rtfMRInf experiment. Between experiment days, they participated in ambulatory mental training, carried out on their smartphones, during which they applied the mental strategies from the experiment, to prolong the learning effects of neurofeedback training. For this publication, only data from the preliminary testing day and the first experiment day (referred to below as 'experiment day') were used.

2.2.2 Preliminary testing day

At the preliminary testing day, we outlined the study procedure to the participants, collected their written informed consent, had them practise four mental stress reduction strategies (see [21] for details), explained the rtfMRInf experiment procedure, and let them familiarize themselves with the Stroop task, but not practise it. Finally, experimenters checked the participants' eligibility with a set of questionnaires and checklists and set an appointment for the *experiment day* (within 1-6 days).

2.2.3 Experiment day

On their second visit, participants performed the neurofeedback experiment where they applied the previously learned mental strategies inside the MRI scanner. The experiment consisted of a series of 3 runs of 8 blocks of the Stroop task (alternated between congruent and incongruent trials) with regular blood pressure measurements (42 times).

The MRI session started with a structural scan to localize the predefined areas for the neurofeedback training (1 min). A functional localizer phase followed (13 min), wherein participants did the Stroop task, to define the individual regions of interest (ROIs). The experiment continued with a resting period (6 min), a "neurofeedback without Stroop" phase (9 min), a resting period, additional structural scans (8 min), a "neurofeedback with Stroop" phase (13 min), another resting period (6 min), a transfer phase with Stroop task but no neurofeedback (13 min), and another resting period (2min).

The "neurofeedback without Stroop" phase allowed us to check for neurofeedback effects in the absence of a stressor, and allowed participants to identify their preferred strategy. To this effect, during the first 4 blocks within that run, we asked participants to use each of the provided strategies in turn (*fixed-strategy* trials), and then to pick one strategy for the remaining 4 runs and also for the rest of the scanner session (*free-choice* trials). The strategies in the first four blocks were: body attention, emotional imagery, facial expression, mantra.

2.2.4 Outcomes and instruments

We defined the following outcome measures: blood-oxygen-level dependent (BOLD) signal as measured in the fMRI and blood pressure (primary), adverse events during the experiment (secondary).

2.2.4.1 Blood pressure acquisition

We measured blood pressure regularly during the fMRI experiments using a *Magnitude 3150M MRI Monitor* and *Millenia 3155MVS* (Invivo, Gainesville, FL, USA), taking eight measurements for each of the experiment's four main phases, two per resting break, and two at the beginning and end of the scanner session.

2.2.4.2 MRI data acquisition

MRI data was recorded using a 3T Siemens Tim Trio scanner with a 12-channel head coil (Erlangen, Germany). We applied a standard gradient echo-planar imaging (EPI) pulse sequence [22]. The EPI parameters were: repetition time (TR) = 1500 ms, echo time = 25 ms, field of view 240*240 mm^2, matrix size 64*64, voxel size = 3.75*3.75*5 mm^3, flip angle 90°, and 30 interleaved slices with 5 mm thickness at approximately 30° oblique to the AC-PC line without a gap [23,24].

2.2.4.3 Questionnaires

To check for inclusion criteria, we used: Edinburgh Handedness Inventory (EHI; [25], Patient Health Questionnaire (PHQ-9; [26], and the Ishihara color test [27] to screen for color-blindness. Feedback on adverse events during the experiment was collected directly after the scanner session. Participants could report *"I had any adverse feelings while in the scanner."* and add details in writing.

2.2.5 Specific procedures

2.2.5.1 Randomization and blinding

We assigned the included participants randomly to either the experimental or control condition, which hence either received feedback from their own rtfMRI signal or sham feedback (signal recorded from another subject). Participants were blinded about their allocation; experimenters were not.

2.2.5.2 Stroop task

To induce stress, we used an adaptive version of the Stroop color-word interference task [28], to be used within the MRI scanner, as previously described elsewhere [16,29]. The main objective in this task is correctly and quickly naming the hue in which a color word (e.g. red, blue) is displayed. In *congruent* trials the words' letters are displayed in the same hue that the words refer to, whereas in *incongruent* trials the two pieces of information (letter hue and word meaning) are different.

2.2.5.3 Mental strategies

We instructed the participants in four mental strategies: i) body attention, ii) emotional imagery, iii) facial expression, and iv) mantra. Details are available elsewhere [21].

2.2.5.4 Neurofeedback protocol and feedback presentation

Whilst lying in the scanner, participants received instructions for the experiment and tasks via the display. Participants wore MRI-compatible binocular goggles (NordicNeuroLab, Bergen, Norway). During the experiment, subjects saw an abstraction of their target ROI brain activity in the form of a thermometer that showed the current relative difference from the ROIs baseline level. Neurofeedback was displayed on one side of the screen, while the Stroop task was visible on the other, when both were present (in the experiment phase "Neurofeedback with Stroop"). Participants also applied the mental strategies simultaneously.

2.2.6 Offline data processing and statistical analysis

2.2.6.1 Software

We used the statistical software packages MATLAB (version R2016a, The MathWorks, Inc., Natick, MA, USA; RRID:SCR_001622) and R (version 3.2.3 and above; RRID:SCR_001905; [30]) for all offline data analysis and statistical testing. We processed and tested fMRI data in MATLAB with the

toolboxes SPM12 (version 6685; RRID:SCR_007037) and MarsBaR (version 0.44; RRID:SCR_009605; [31]) and calculated mixed effects models with R.

2.2.6.2 fMRI data processing

We preprocessed the acquired EPI volumes in SPM12 as follows: head motion correction, spatial normalization into Montreal Neurological Institute (MNI) space, and spatial smoothing with an 8 mm isotropic full width at half maximum (FWHM) Gaussian kernel.

We ran first-level subject-wise general linear models (GLMs) in SPM12 with incongruent and congruent Stroop task trials as parameters and this contrast: higher activity in incongruent compared to congruent Stroop task trials (t-contrast [-1 1]). SPM first-level models perform a linear regression for each voxel, employing generalized least squares with a global approximate AR(1) autocorrelation model, and Discrete Cosine Transform basis with a 128 second cut-off to fit drift. All results were assessed at $p<0.05$, family-wise error rate (FWE) corrected voxel-wise over the whole brain, for all reported fMRI models.

We extracted ROI parameters from the results of the 1st level GLM models with the MarsBaR region of interest toolbox for SPM (version 0.44; RRID:SCR_009605; [31]). To do this, we created two combined ROIs for the whole ACC and IC, out of the left and right ACC and IC templates from the AAL ROI library [19] adaptation in SPM/MarsBaR (RRID:SCR_003550) and extracted the mean signal over all voxels within the ROIs.

2.2.6.3 Linear mixed effects models for fMRI and blood pressure

We calculated linear mixed effects models (LMMs) to address the longitudinal nature of the data. On the extracted fMRI time series and blood pressure as outcomes, we ran separate LMMs: In the experiment phase "neurofeedback without Stroop", we set fixed effects *trial* and *subphase* (fixed-strategy trials vs. free-choice trials) and random intercepts for the participants. In the experiment phases ’functional localizer’ and ’neurofeedback with Stroop’ we set fixed effects *Stroop* (all measurements during incongruent versus congruent trials) and *block* (pairs of one incongruent and the following congruent Stroop trial) and random intercepts for the participants.

To check differences between the experimental and control conditions, we added the main effect *condition*, and the interaction terms *Stroop*condition* in the “neurofeedback with Stroop” phase, and *subphase*condition* in “neurofeedback without Stroop”, as fixed effects. The described effects and

variables are illustrated in Figure S1 (Panel B), within the experimental design of the individual phases. Additional to beta estimates, t and p-values, we report 95% confidence intervals (CIs) calculated via the Wald method. All conducted tests were two-tailed and assessed at a significance level of 0.05.

2.2.6.4 Correlations between blood pressure and neural activity

As exploratory analyses to investigate whether the *learning effect* during "neurofeedback with Stroop" – the change in the Stroop effect over trials (interaction Stroop*block) – was associated in the fMRI and blood pressure data, we calculated Pearson's product-moment correlation coefficients between the extracted learning effect values from individual LMMs. These were random-effects-only models, which enabled the extraction of individual parameters for each subject, and included the relevant interaction which was extracted (Stroop*trial) and the related two main effects, all as random effects over subjects. Similarly, for the "neurofeedback without Stroop" phase, we extracted the main effect of subphase from such mixed models. Outliers were removed for each individual correlation based on Cook's distance with a threshold of 4/n [32].

3 Results

3.1 Sample description and participant flow

Please find the flow of participants through our study in Figure S5. We conducted the experiment between August and October 2013. Of the initially 31 subjects included in the study, we used data of 30 subjects (17 in experimental condition, 13 in control condition), because one subject did not show up for the fMRI experiment. All participants were of Korean nationality; healthy young men from 20 to 30 years of age. Table S1 reports the characteristics of the study sample. The two groups showed no significant differences in their sociodemographic characteristics.

3.2 Stressor-evoked fMRI activity

Activity maps over all 30 participants for the contrast "incongruent > congruent Stroop trials" are presented in Figure S6 and in more detail in separate tables (S2, S3) in the Supplement materials. Activity differences due to the Stroop effect during the "functional localizer" phase were pronounced in clusters in the right supplementary motor area, the left and right superior parietal lobule, right IC, right middle occipital gyrus, and the right opercular part of the inferior frontal gyrus. During

"neurofeedback with Stroop", we found the largest activation clusters in the right angular gyrus, the left middle occipital gyrus, and the left opercular part of inferior frontal gyrus.

3.3 Stressor-evoked blood pressure reaction

Detailed results of the LMMs of the blood pressure data can be found in Table 1 and descriptive values in Figure 1. For the functional localizer phase, they indicate a significant Stroop effect with higher values during the incongruent as compared to congruent Stroop trials for both blood pressure values. For the diastolic values, we found this Stroop effect also in the phase “neurofeedback with Stroop”, though much less pronounced.

There was further a continuous decrease in the blood pressure reaction to the Stroop task the more often the task was repeated, as is visible in the block effect within the functional localizer phase.

3.4 rtfMRInf

The descriptive data of the time series of the ROI activity (Figure 2) suggest group differences in the "neurofeedback without Stroop" phase: subjects in the experimental condition showed a decrease in the ROI activity over the phase, especially after the fixed strategy trials, while those in the control group showed increased activity after a drop in the fourth trial of the phase (Figure 2 A). The mixed models support this, indicating a significant difference in the subphase effect (fixed-strategy vs. free-choice strategy trials, Figure 2 B): subjects in the experimental condition had lower relative activity when using a strategy of their choice compared to those in the control condition. This interaction was present in both ACC and IC. In the phase "neurofeedback with Stroop", we found a significant interaction between the Stroop effect and the condition in the ACC, with the brain activity being significantly less increased during the incongruent Stroop trials in comparison to congruent trials, for participants in the experimental condition (see Table 2, Figure 3).

Mixed models of the blood pressure data (see Table 1) showed no significant differences between the two condition groups for the Stroop effect.

3.5 Correlation between fMRI activity and blood pressure

Exploratory analyses results of correlations between the ROI activity time series and mean blood pressure values are presented in Figure S7. When looking at the individual decrease of the Stroop effect during the phase "neurofeedback with Stroop", the learning effect (interaction Stroop*block),

diastolic blood pressure was significantly correlated with activity in the IC in the experimental condition ($r(14)=0.567$, $p=0.0220$), but not in the control condition ($r(10)=0.268$, $p=0.399$).

Similarly, for the subphase effect and during "neurofeedback without Stroop", diastolic blood pressure was significantly correlated with activity in the IC ($r(14)=0.777$, $p=3.96 \times 10^{-4}$) and the ACC ($r(14)=0.846$, $p=3.69 \times 10^{-5}$) in the experimental condition, but not in the control condition ($r(10)=-0.332$, $p=0.292$; $r(10)=-0.373$, $p=0.233$).

3.6 Adverse events during neurofeedback training

What we report are events that may represent unintended side-effects, as these were any adverse feelings participants reported after the experiment. None of these were serious adverse events as defined in the Code of Federal Regulations [33].

24 of the 30 participants (80%) reported no events during the training, while five did (17%) and one participant (3%) didn't answer the question. Three participants in the control condition reported task-related events (*"Too long task not enough time to response", "it's more harder than I think before the experiment", "I felt the bar moves differently with my thought or strategy")*, while two participants in the experimental condition reported other events unrelated to the task (*"so sick", "a little uncomfortable"*). We applied Fisher's exact tests to check for differences between the conditions in these frequencies. There were no significant differences for all reported adverse events ($p=0.63$), for the task-related events ($p=0.07$), or the other reported events ($p=0.49$).

4 Discussion

We investigated whether fMRI neurofeedback could reduce stress-related brain activity and blood pressure reaction and found the following: Without a stressor present, brain activity during neurofeedback training was lower in the experimental condition when participants used a mental strategy of their choice compared to when they were told which strategy to use. With a stressor, subjects in the experimental condition showed a significantly smaller stress effect than those in the control condition, in line with our hypothesis. However, this was only the case in one of the two tested brain regions, the ACC. Regarding blood pressure values, we found no difference among

conditions during any neurofeedback trials. There was also no difference between the conditions regarding adverse events.

Exploratory analysis into correlations between brain activity and blood pressure indicated that a learning effect was partly correlated in the experimental condition but not in the control condition, in diastolic blood pressure values.

The identified difference among conditions during neurofeedback without a stressor partly supports our first hypothesis, that during neurofeedback, brain activity would be lower for experimental participants in the target regions. Notably, we only found evidence for different brain activity with regard to the difference between fixed-strategy and free-choice trials. How can we explain this? One explanation highlights the cognitive capacity needed to focus on a specific strategy: When participants were told which strategy to use, they might have been concerned with remembering and following the strategy, which decreased their focus on neurofeedback. When free to choose the strategy, they chose one which allowed more focus on the feedback training. This helped those in the experimental condition to decrease their activity, but not those who received sham feedback. It is also possible that neurofeedback works better when subjects are not given a specific strategy. Whether or not giving participants an explicit strategy for neurofeedback training is an open discussion [9,34]; in one study neurofeedback worked equally well or better without explicit strategy [35].

In line with our second hypothesis, our main finding during neurofeedback with a stressor indicated that participants in the experimental condition had a relatively reduced stress response in their ROI activity compared to those in the control condition. This was only evident in the ACC, which may be based on the ACC being more receptive for neurofeedback in the context of stress regulation, though that requires further study.

Regarding our third hypothesis, we found no differences in blood pressure reactivity between conditions. Potentially a consequence of habituation effects: While subjects did show blood pressure increases during the first Stroop task (functional localizer phase), these dwindled quickly with repetition. To avoid this, future studies could use a different stressor task which more reliably induces a stress response when repeated many times in close succession. The *Montreal Imaging Stress Task* might be a good candidate here [36].

The secondary outcome, adverse events, showed now difference between the two conditions and no severe adverse events were reported. The safety of rtfMRInf should, however, be investigated further, especially in regard to applications in clinical samples.

The identified correlations between individual brain activity and blood pressure values related to the task were all with diastolic blood pressure and only for the experimental condition. This might indicate that the learned modulation of brain activity over time was individually similar to the learned modulation of blood pressure, but only when real neurofeedback was given.

Even though we found some indication that rtfMRInf can influence the stress response, further investigation might elucidate its potential to modulate other downstream consequences of central neuronal stress-reactivity (e.g., cortisol, immune system) and to increase coupling of central and peripheral stress reactivity.

Our study had several specific strengths: We instructed participants in several mental strategies and beyond fixed mental strategies, we allowed participants to choose freely among them. We also used a functional localiser phase to identify individual stress-related brain activity instead of working with the same generic ROIs for all participants, to provide a more individualized feedback signal. Our study design further allowed the comparison of neurofeedback effects under stress-exposure (Stroop) and without a stressor present. We also used well described, clinically relevant paradigm to elicit stress. Limitations of our study include the fact that contingent feedback may also be linked to mental strain itself (double task), as indicated by a tendency for generally higher blood pressure responses to the stressor throughout the experiment (absolute values). Also, the blood pressure response to the stressor decreased quickly with repetition of the task. The quick habituation of the cardiovascular response to the stressor might have diminished the peripheral stress response before the neurofeedback training had started.

All results must be considered within the limits of our sample characteristics. Given that we only included healthy men within a rather narrow age range (20-30) who were all students at Korea University, future studies are needed to further explore the generalizability of our findings, including subjects suffering from stress-related disorders.

To improve future experimental designs, we further suggest: Recent developments in the field turns towards using activity from a whole network of interacting brain areas instead of using the signal from only one or two predefined target ROIs [37–39]. A promising approach further suggests using

biomarkers based on resting-state functional connectivity MRI [40]. Since giving explicit instructions to the participants during the neurofeedback training might actually decrease the subjects' ability to learn to control the target region [9,35], future studies would benefit from addressing this issue, e.g. by creating two separate experimental conditions in which the participants either do or do not get explicit instructions for neurofeedback training.

5 Conclusion

To the best of our knowledge, this is the first study reporting real-time fMRI neurofeedback to reduce stress-related brain activity. Participants could further reduce their response to the stressor directly, in one out of two target brain regions (ACC). While these findings did not transfer to blood pressure reactivity, rtfMRInf was linked to coupling of learning effects in brain and cardiovascular stress responses, suggestive of rtfMRInf potentially enhancing peripheral outcomes of interventions targeting the brain.

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Statement of Ethics

All participants gave their written informed consent and the study protocol was approved by the Korea University's institutional board (approval number: KU-IRB-10-38-A-2(E-A-1)(E-A-1)(E-A-3)).

Disclosure Statement

GM has been acting as consultant for Janssen Research & Development, LLC. The authors have no conflicts of interest to declare.

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Author Contributions

AB (Data Curation, Formal Analysis, Methodology, Software, Visualization, Writing – Original Draft Preparation, Writing – Review & Editing); JL (Conceptualization, Data Curation, Investigation, Methodology, Project Administration, Resources, Software, Supervision, Writing – Review & Editing); HK (Investigation, Software, Writing – Review & Editing); ES (Data Curation, Writing – Review & Editing); EKJ (Investigation, Software, Writing – Review & Editing); MO (Data Curation, Investigation, Writing – Review & Editing); SY (Conceptualization, Methodology, Resources, Writing – Review & Editing); JCP (Conceptualization, Methodology, Writing – Review & Editing); MT (Conceptualization, Data Curation, Funding Acquisition, Methodology, Project Administration, Resources, Supervision, Writing – Review & Editing); GM (Conceptualization, Data Curation, Methodology, Project Administration, Resources, Supervision, Writing – Review & Editing)

Figure Legends

Fig. 1. Blood pressure data in neurofeedback phases with and without Stroop. Mean systolic and diastolic values for each measurement for experimental and control condition.

Fig. 2. fMRI ROI time series data in phase “Neurofeedback without Stroop”. (A) Mean activity in both ROIs by condition for fixed-strategy and free-choice trials. (B) Mean signal difference between fixed-strategy and free-choice trials (“Subphase effect”).

Fig. 3. fMRI ROI time series data in phase “Neurofeedback with Stroop”. (A) Mean activity in both ROIs by condition. (B) Mean signal difference between incongruent and congruent Stroop trials (“Stroop effect”).

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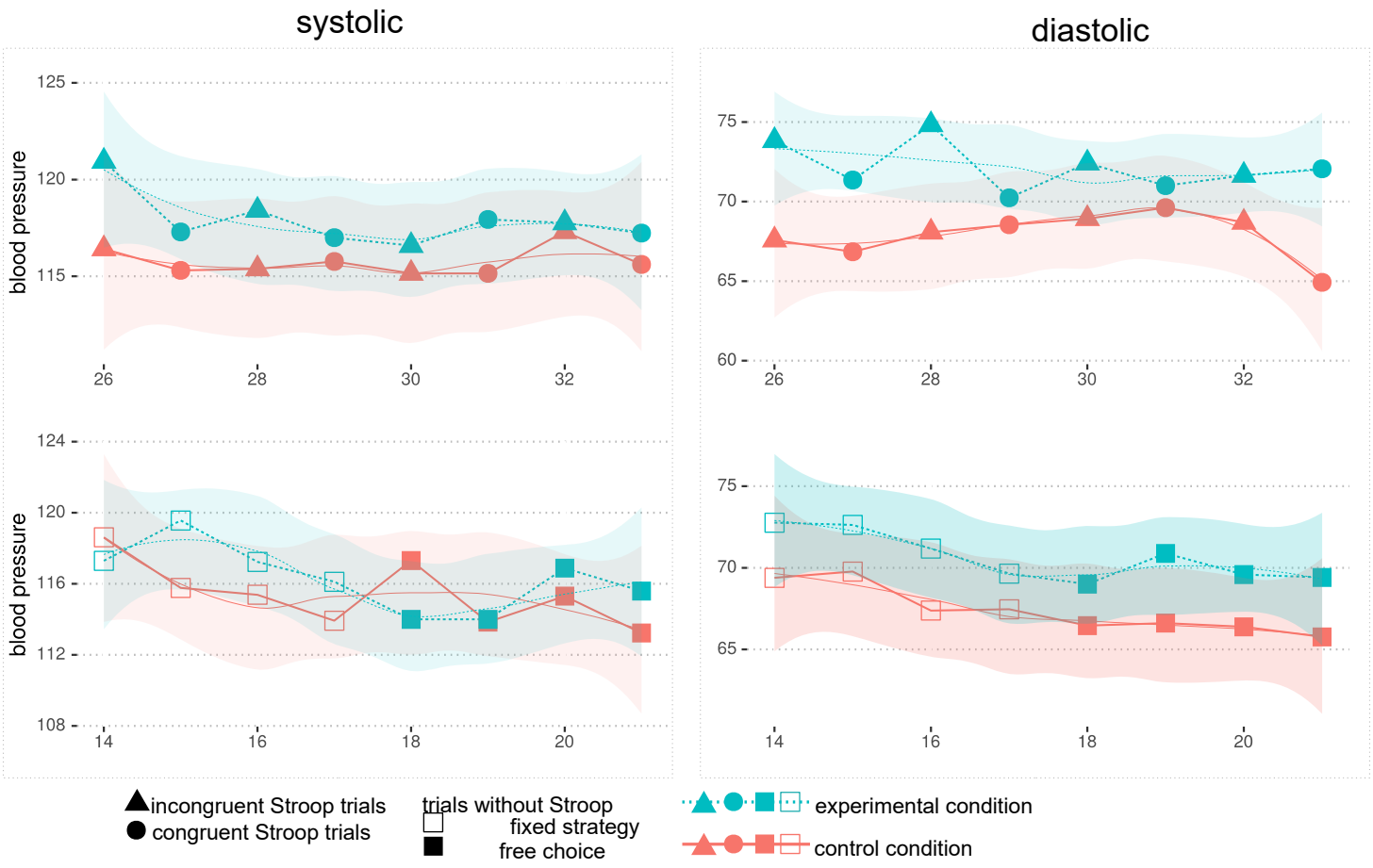
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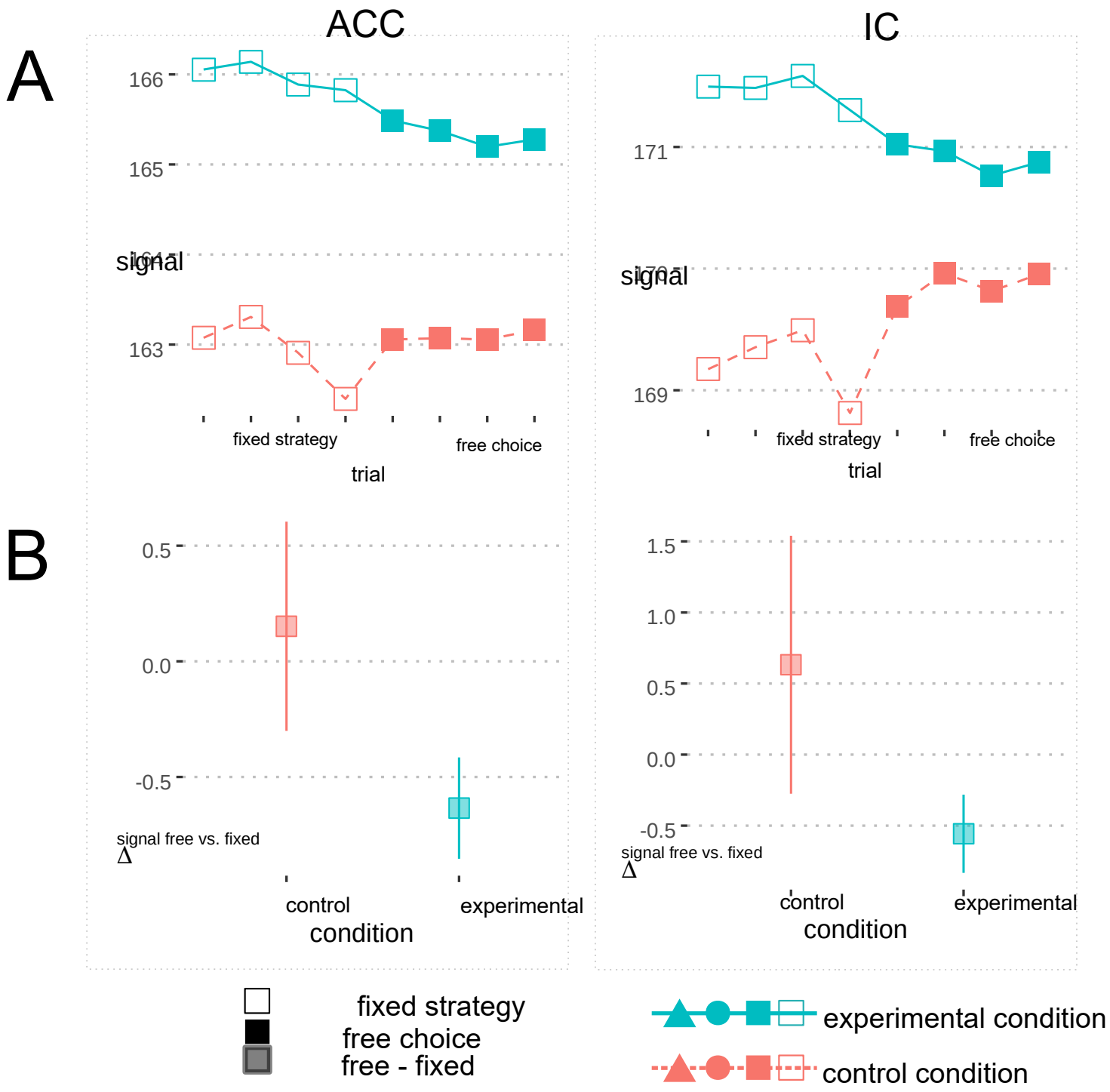
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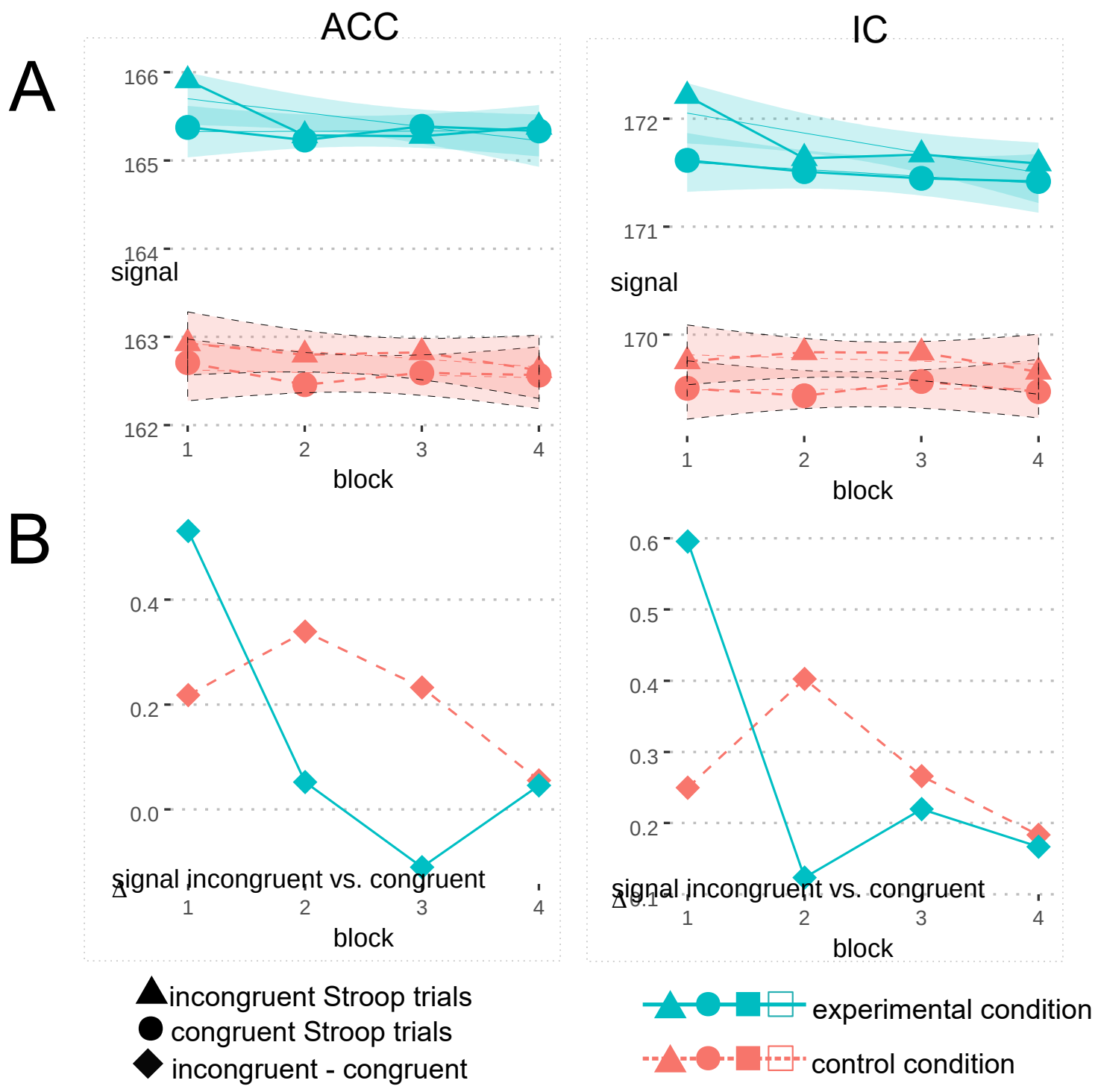
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Table 1. *LMM results for blood pressure*

	Diastolic blood pressure					Systolic blood pressure			
Phase: Neurofeedback with Stroop									
Predictors	*Estimates*	*95%CI*	*p*		*Predictors*	*Estimates*	*95%CI*	*p*	
(Intercept)	70.11	67.41; 72.82	**3.15E-29**	***	(Intercept)	116.95	113.96; 119.94	**3.88E-34**	***
Stroop Incongruent	0.78	0.31; 1.26	**1.53E-03**	**	Stroop Incongruent	0.49	-0.06; 1.03	0.08	
Condition Experimental	1.99	-0.64; 4.63	0.15		Condition Experimental	0.65	-2.26; 3.56	0.66	
Block	-0.26	-0.72; 0.21	0.29		Block	-0.32	-0.81; 0.18	0.21	
Stroop*Condition	0.22	-0.25; 0.70	0.36		Stroop*Condition	0.04	-0.50; 0.58	0.88	
Stroop*Block	-0.22	-0.64; 0.21	0.32		Stroop*Block	-0.37	-0.85; 0.11	0.13	
Phase: Neurofeedback without Stroop									
Predictors	*Estimates*	*95%CI*	*p*		*Predictors*	*Estimates*	*95%CI*	*p*	
(Intercept)	68.97	65.98; 71.96	**9.26E-28**	***	(Intercept)	115.83	112.96; 118.70	**1.89E-34**	***
Subphase Free choice	0.07	-0.89; 1.02	0.89		Subphase Free choice	0.14	-1.16; 1.43	0.84	
Condition Experimental	1.56	-1.39; 4.51	0.31		Condition Experimental	0.61	-2.25; 3.48	0.68	
Trial	-0.51	-0.99; -0.03	**0.04**	*	Trial	-0.48	-1.05; 0.08	0.10	
Subphase*Condition	0.13	-0.50; 0.76	0.68		Subphase*Condition	-0.33	-0.98; 0.31	0.31	

To increase interpretability of the main effects, we centered numeric predictor variables and coded factors variables using effect/deviant coding, so that the effects are compared to the mean intercept. This simplifies comparison over phases and interpretation of main effects when including interactions in the models. In interaction terms, the factor levels are the same as in the main effects (e.g. interaction Stroop*Condition means Stroop incongruent trials * Condition experimental).

Table 2. LMM results for fMRI ROI time course data

	ROI ACC					ROI IC			
Phase: Neurofeedback with Stroop									
Predictors	*Estimates*	*95%CI*	*p*		*Predictors*	*Estimates*	*95%CI*	*p*	
(Intercept)	164.06	162.39; 165.73	**6.21E-48**	***	(Intercept)	170.66	169.22; 172.10	**2.28E-50**	***
Stroop Incongruent	0.08	0.07; 0.09	**1.64E-33**	***	Stroop Incongruent	0.13	0.12; 0.14	**6.18E-96**	***
Condition Experimental	1.35	-0.32; 3.03	0.123		Condition Experimental	0.92	-0.51; 2.35	0.218	
Block	-0.06	-0.14; 0.02	0.147		Block	-0.07	-0.17; 0.03	0.189	
Stroop*Condition	-0.03	-0.04; -0.01	**3.29E-05**	***	Stroop*Condition	-0.01	-0.02; 0.01	0.270	
Stroop*Block	-0.06	-0.07; -0.05	**2.96E-23**	***	Stroop*Block	-0.04	-0.05; -0.03	**6.47E-14**	***
Phase: Neurofeedback without Stroop									
Predictors	*Estimates*	*95%CI*	*p*		*Predictors*	*Estimates*	*95%CI*	*p*	
(Intercept)	164.33	162.53; 166.13	**4.66E-47**	***	(Intercept)	170.36	168.84; 171.88	**1.14E-49**	***
Subphase Free choice	0.07	0.03; 0.11	**3.37E-04**	***	Subphase Free choice	0.09	0.05; 0.13	**4.06E-06**	***
Condition Experimental	1.3	-0.47; 3.08	0.160		Condition Experimental	0.82	-0.70; 2.33	0.299	
Trial	-0.1	-0.19; 0.00	0.059		Trial	-0.04	-0.21; 0.13	0.655	
Subphase*Condition	-0.22	-0.26; -0.18	**1.04E-27**	***	Subphase*Condition	-0.27	-0.31; -0.23	**1.08E-40**	***

To increase interpretability of the main effects, we centered numeric predictor variables and coded factors variables using effect/deviant coding, so that the effects are compared to the mean intercept. This simplifies comparison over phases and interpretation of main effects when including interactions in the models. In interaction terms, the factor levels are the same as in the main effects (e.g. interaction Stroop*Condition means Stroop incongruent trials * Condition experimental).

Supplement with comprehensive materials and methods section for

"Real-time fMRI Neurofeedback to Modulate the Neural and Cardiovascular Stress Response: A Randomized Controlled Trial"

by Angelo Belardi, Jong-Hwan Lee, Hyun-Chul Kim, Esther Stalujanis, Eun Kyung Jung, Minkyung Oh, Seung-Schik Yoo, Jens C. Pruessner, Marion Tegethoff, Gunther Meinlschmidt

Comprehensive materials and methods section

(This text includes parts of the materials and methods section in the main manuscript, but has added information which is marked here in a maroon font.

1.1 Participants

We recruited participants from the student body of the Korea University by posting ads for the study on the university website and a local bulletin board. We assessed the applicants eligibility based on the following criteria: male, 18-65 years old, right-handedness, no color-blindness, no history of cardiovascular or neurological diseases or severe mental disorders, sufficient English language skills to follow the experimental instructions, and familiarity with smartphone-use to carry out the ambulatory training (which is in more detail explained in [1]).
All participants gave their written informed consent and Korea University's institutional board approved the study protocol. After the experiment, participants received 60 000 KRW (≈57 USD) in compensation for their efforts.

We decided about the sample size based on the results of earlier studies which found large effect sizes for rtfMRInf [2,3]. With a power analysis we determined that we could detect effects with a Cohen's d of 1.0 with sufficient power ($1 - \beta > .80$; with $\alpha = 0.05$, one-sided) if we had 14 subjects in each group. We stopped recruiting after reaching the intended 30 participants with at least 14 participants allocated to each condition.

1.2 Outline of study procedures

1.2.1 Overall study procedure

We conducted a block-randomised parallel-group neurofeedback study with a sham-feedback control condition and participants blinded to their allocation. The study reported in this publication was registered in the online registry for clinical trials ClinicalTrials.gov with the identifier NCT01921088. The whole study consisted of three laboratory visits and 13 days of individual ambulatory mental training. We first screened applicants in a telephone interview for any history of neurological or mental disorders and invited those suitable to a laboratory visit, the *preliminary testing day*, to verify whether they met all inclusion criteria outlined above.

Included applicants visited the laboratory twice (14 days apart) for the main rtfMRInf experiment. Between experiment days, they participated in ambulatory mental training, carried out on their smartphones, during which they applied the mental strategies from the experiment, to prolong the learning effects of neurofeedback training.

For this publication, only data from the preliminary testing day and the first experiment day (referred to below as 'experiment day') were used.

1.2.2 Preliminary testing day

At the preliminary testing day, we outlined the study procedure to the participants, collected their written informed consent, had them practise four mental stress reduction strategies [for details, see 1], explained the rtfMRInf experiment procedure and neurofeedback

presentation, and let them familiarize themselves with the Stroop task, but not practise it. Finally, experimenters checked the participants' eligibility with a set of questionnaires and checklists and set an appointment for the *experiment day* (within 1-6 days) .

1.2.3 Experiment day

On their second visit, participants performed the neurofeedback experiment where they applied the previously learned mental strategies inside the MRI scanner. The experiment consisted of a series of 3 runs of 8 blocks of the Stroop task (alternated between congruent and incongruent trials) with regular blood pressure measurements (42 times).

The MRI session started with a structural scan to localize the predefined areas for the neurofeedback training (1 min). A functional localizer phase followed (13 min), wherein participants did the Stroop task, to define the individual regions of interest (ROIs). The experiment continued with a resting period (6 min), a "neurofeedback without Stroop" phase (9 min), a resting period, additional structural scans (8 min), a "neurofeedback with Stroop" phase (13 min), another resting period (6 min), a transfer phase with Stroop task but no neurofeedback (13 min), and another resting period (2min). The experimental procedure is given in Figure S4.

The "neurofeedback without Stroop" phase allowed us to check for neurofeedback effects in the absence of a stressor, and allowed participants to identify their preferred strategy. To this regard, during the first 4 blocks within that run, we asked participants to use each of the provided strategies in turn (*fixed-strategy* trials), and then to pick one strategy for the remaining 4 runs and also for the rest of the scanner session (*free-choice* trials). The strategies in the first four blocks were: body attention, emotional imagery, facial expression, mantra.

1.2.4 Outcomes and instruments

We defined the following primary outcome measures: blood-oxygen-level dependent (BOLD) signal as measured in the fMRI and blood pressure. As secondary outcome, we asked the participants about adverse events during the experiment after the fMRI session.

1.2.4.1 Blood pressure acquisition

We measured blood pressure regularly during the fMRI experiments using a *Magnitude 3150M MRI Monitor* and *Millenia 3155MVS* (Invivo, Gainesville, FL, USA), taking eight measurements for each of the experiment's four main phases, two in each resting break, and two more each at the beginning and end of the scanner session.

Each recording took around 40-60 s and each series of assessments was started (cuff inflation) 25 s into the block of trials of the different main phases of the experiment. Of these measurements, we obtained printouts from the blood pressure monitor and hand-recorded logs of the values as displayed during the recording. The printouts were not always clearly legible which is why we additionally manually logged the values. Two independent research assistants entered these measurements (systolic, diastolic, and mean arterial pressure (MAP) each) into electronic spreadsheets. A third research assistant then cross-checked the entries. Differences were resolved in discussion. We relied first on the printouts and only checked the hand-written logs to clarify ambiguous entries.

1.2.4.2 MRI data acquisition

MRI data was recorded using a 3T Siemens Tim Trio scanner with a 12-channel head coil (Erlangen, Germany). To assess the BOLD intensity associated with neuronal activity, we applied a standard gradient-echo EPI pulse sequence [4]. The EPI parameters were: repetition time (TR) = 1500 ms, echo time = 25 ms, field of view 240*240 mm^2, matrix size 64*64, voxel size = 3.75*3.75*5 mm^3, flip angle 90°, and 30 interleaved slices with 5 mm thickness at approximately 30° oblique to the AC-PC line without a gap [5,6].

1.2.4.3 Questionnaires

To check for inclusion criteria, we used: Edinburgh Handedness Inventory (EHI; [7], Patient Health Questionnaire (PHQ-9; [8] to screen for depression, and the Ishihara color test [9] to screen for color-blindness. Feedback on adverse events during the experiment was collected directly after the scanner session, as part of a self-report questionnaire. The statement was *"I had any adverse feelings while in the scanner."*, with response-choice 'yes/no', followed by empty lines to write down details about the adverse event.

1.1.1 Specific procedures

1.1.1.1 Randomization and blinding

We assigned the included participants randomly to either the experimental or control condition, which hence either received feedback from their own rtfMRI signal or sham feedback (with the feedback signal recorded from another subject). Each control group participant was paired with one of the experimental participants, from whom the recording was used as sham feedback.

To maintain close to a 1:1 allocation ratio among the two conditions over the course of the study, we randomized the subjects in three blocks of 8, 10, and 12 (block randomization), whose ordering was chosen at random. Thus, we applied a random permutation function in MATLAB, which is based upon a random number generator that uses the *Mersenne Twister* algorithm [10]. Randomization was carried out by a researcher not involved in conducting the experiment or processing the data and without contact with the participants at any stage, who then created a list of participant numbers with their condition allocations based on this randomization. This researcher also concealed the allocations from the researchers based at Korea University which were involved in recruiting and assigning of the participants. Allocation to either of the conditions, based on the preset list of participant numbers, was not done until a final decision about inclusion in the experiment was carried out on the preliminary testing day. Once we decided to include a participant, we assigned him the next participant number and its linked condition group.

Participants were blinded about their allocation until completion of the study. Experimenters were not blinded to the allocation, since they had to either provide the subjects with the feedback signal from the subjects own neuronal activity, or replay a recording of the signal of a previous participant. Researchers who entered blood pressure data recordings or questionnaire information to their digital form were blinded to the condition allocation of the participants at the time. Data analysts of offline analyses were aware of the allocation.

1.1.1.2 Stroop task

To induce stress, we used an adaptive version of the Stroop color-word interference task [11], to be used within the MRI scanner, as described before in [12,13]. The main objective in this task is correctly and quickly naming the hue in which a color word (e.g. red, blue) is

displayed. In *congruent* trials the words' letters are displayed in the same hue that the word refers to, whereas in *incongruent* trials the two pieces of information (letter hue and word meaning) are different. Incongruent trials elicit a higher cognitive demand than congruent trials, and lead to a psychobiological stress response, which is detectable in both, blood pressure and BOLD activity changes [13,14].

Regarding the adaption of the Stroop task for its use in the MRI scanner, the main difference was how subjects provided the answers: Participants gave their answers by selecting from a set of choices on a fiber-optic response pad (Current Design, Philadelphia, PA; www.curdes.com). They operated the device with their right hand.

To make it more challenging, we used a Stroop task that was made adaptive to the participant's performance [13,14]. The adaptations are as follows: The accuracy to identify target words was kept at a level of 60% by adjusting the trial presentation times. For example, when the participant improved his performance in an incongruent block, the allowed response time in the following trial was shortened. Allowed response times ranged between 1 and 5 seconds [15]. Additionally, the number of trials in each congruent block was linked to that of the completed trials in the preceding incongruent block.

1.1.1.3 Mental strategies

We instructed the participants in four mental strategies: i) body attention, ii) emotional imagery, iii) facial expression, and iv) mantra. Details are available elsewhere [1].

These strategies had in similar form been applied in psychotherapy to address affective and anxiety disorders [16–20] and had already been found to reduce stress responses or hypertension: Transcendental Meditation (similar to our mantra strategy) decreased blood pressure in patients with hypertension according to a meta-analysis [21]. Mindfulness meditation had an effect on psychological stress according to another meta-analysis [22], and a combination of body-mind techniques including breath adjustment, mental imagery, and mindfulness training reduced stress-induced cortisol levels in a guided intervention of 20 minutes for five days [23]. Similar strategies had also been shown to decrease blood pressure [24,25].

1.1.1.4 Neurofeedback protocol and feedback presentation

Whilst lying in the scanner, participants received instructions for the experiment and tasks via the display. Participants wore MRI-compatible binocular goggles (NordicNeuroLab, Bergen, Norway) to see the screen. During the experiment, subjects saw an abstraction of their target ROI brain activity in the form of a thermometer that showed the current relative positive or negative difference from the ROIs baseline level.

Based on established findings for neuronal correlates of stress responses in the Stroop task [13,26], we defined a set of anatomical regions of interest (ROIs) to use as the target regions for our neurofeedback training. These regions comprised the left and right ACC and left and right IC from the AAL ROI library [27]. We had a backup set of ROIs, in case there was no activity present in any voxels within the first set. The backup set added the left and right superior frontal gyrus and medial orbital frontal gyrus.

For the neurofeedback training, we instructed participants to modulate the neural activity in the target regions (by applying the learned mental strategies) with the following: *"You will see a white moving bar. The level of the bar represents your current brain activity which is*

indicative of your stress level: the higher the bar, the higher your stress level. Your goal is to lower the bar and to keep the bar as low as possible. You will also see a grey line that indicates how you performed during the past round, so you should definitely stay well below the grey line.“

Additional instructions were displayed before the training to increase the stress induction: *“We adjusted this task to the average performance of SKY students. Therefore, we assume and hope that the difficulty of the task is fine for you. We ask you to do the best you can during the task. We will observe your performance from the control room.“* Please note that “SKY” is an acronym for the three top-ranking national higher-education institutions in the Republic of Korea.

1.1.1.5 Online data processing and feedback signal calculation

The code for rtfMRInf signal calculation and presentation was developed in-house and written in MATLAB, updated from previous versions which were reported elsewhere [3,28–32]. It ran on a notebook (Specifications: Intel Core i5 2.4 GHz, 8 GB RAM, 256 GB SSD; OS: Windows 7) that was via a TCP/IP link connected to the MRI scanner’s console computer – which reconstructed the raw EPI volumes – to transfer the raw EPI volumes in real-time, to then visualize and feed back the signals to the subjects.

During a complete set of eight Stroop task trials (four blocks of a congruent and incongruent trial), the “functional localizer” phase, the ROIs were then pinpointed to ensure that for each subject only the activity most associated with the task was used as feedback signal for the neurofeedback training blocks.

We preprocessed the EPI data from the functional localizer phase with the following sequence: realignment to correct six head motion parameters, spatial smoothing with an 8 mm full-width at half maximum Gaussian kernel. Next, we used the preprocessed EPI data to estimate beta-value maps of each of the incongruent and congruent Stroop trials using the general linear model (GLM) implemented in SPM and obtained a contrast map for "incongruent > congruent Stroop trials". To calculate the neurofeedback signal, we then used the intersection map between ROIs from the GLM and the predefined set of ROIs.

To create the neurofeedback information, we first removed possible artifacts from the raw BOLD signal of all voxels within the ROIs: To avoid low-frequency linear drift [4], we applied a bandpass-filter (0.008 - 0.1 Hz) using a third-order elliptic digital filter adapted in MATLAB.

We then took the median BOLD signals within each of the ROIs as well as the whole-brain area and linearly detrended them. We averaged the values between the 10th and 30th percentile during the cross-fixation period (30-40 s) and used that as the baseline BOLD intensity for the ROIs and the whole-brain area. Percentage BOLD signal change (PSC) of the ROIs relative to the whole-brain was estimated in a voxel-wise manner, by subtracting the PSC estimated in the whole-brain area from that in the ROI. This relative value was used as the neurofeedback signal.

To reduce potential high-frequency fluctuations due to non-neuronal components such as cardiac-and respiratory-related fluctuations, we averaged the PSC values for the last three TR periods.

1.1.2 Offline data processing and statistical analysis

1.1.2.1 Software

We used the statistical software packages MATLAB (version R2016a, The MathWorks, Inc., Natick, MA, USA; RRID:SCR_001622) and R (version 3.2.3 and above; RRID:SCR_001905) [33] for all offline data analysis and statistical testing. We processed and tested fMRI data in MATLAB with the toolboxes SPM12 (version 6685; RRID:SCR_007037) and MarsBaR (version 0.44; RRID:SCR_009605) [34] and calculated mixed effects models with R.

Besides basic R functions and packages, we added these R packages for specific purposes as follows: "lme4"(Bates et al., 2014), "optimx" (Nash and Varadhan, 2011), and "lmerTest" for mixed effects models; "ggplot2" "ggpubr", and "gridExtra" to create data visualizations; "reshape", "tidyr", "dplyr", for data preparation and descriptive statistics; "sjPlot" to format mixed models results tables.

1.1.2.2 fMRI data processing

We preprocessed the acquired EPI volumes in SPM12, applying the following steps and parameters, in this order: head motion correction, spatial normalization into MNI space, and spatial smoothing with an 8 mm isotropic full width at half maximum (FWHM) Gaussian kernel.

First-level subject-wise GLMs were run in SPM12 with incongruent and congruent Stroop task trials as parameters. We tested the following contrast: Higher activity in incongruent compared to congruent Stroop task trials (t-contrast [-1 1]). SPM first-level models perform a linear regression for each voxel, employing generalized least squares with a global approximate AR(1) autocorrelation model, and Discrete Cosine Transform basis with a 128 second cut-off to fit drift. All results were assessed at $p<0.05$, family-wise error rate (FWE) corrected voxel-wise over the whole brain, for all reported fMRI models.

We extracted ROI parameters from the results of the 1st level GLM models with the MarsBaR region of interest toolbox for SPM (version 0.44; RRID:SCR_009605) [34]. To do this, we created two combined ROIs for the whole ACC and IC, out of the left and right ACC and IC templates from the AAL ROI library [27] adaptation in SPM/MarsBaR (RRID:SCR_003550) and extracted the mean signal over all voxels within the ROIs.

1.1.2.3 Linear mixed effects models for fMRI and blood pressure

We calculated linear mixed effects models (LMMs) to address the longitudinal nature of the data and the underlying assumption that values from the same participants are more similar than those from other participants. On the extracted fMRI time series and blood pressure as outcomes, we ran separate LMMs as follows: In the experiment phase "neurofeedback without Stroop", we set fixed effects *trial* and *subphase* (fixed-strategy trials vs. free-choice trials), and added random intercepts for the participants. In the experiment phases "functional localizer" and "neurofeedback with Stroop" we set fixed effects *Stroop* (all measurements during incongruent versus congruent trials) and *block* (pairs of one incongruent and the following congruent Stroop trial), and added random intercepts for the participants.

To check differences between the experimental and control conditions, we added the main effect *condition*, and the interaction terms *Stroop*condition* in the "neurofeedback with Stroop" phase, and *subphase*condition* in "neurofeedback without Stroop", as fixed effects.

The described effects and variables are illustrated in Figure S4 (Panel B), within the experimental design of the individual phases.

We selected these final mixed effects models from a set of theoretically derived models, which reflect the experiment design of the individual experiment phases. We based the selection on comparison tests using the Satterthwaite approximation, which suggested the model with the lowest AIC values. Following these test results, we consequently chose those models with the lowest AIC values, with one exception: for the blood pressure models in "neurofeedback with Stroop" we selected random slope models as well, even though the AIC for the random intercept only model had a slightly smaller AIC value (though was not significantly better than this model), to ensure more similarity to the models applied on brain activity data, we used in this phase (with the fmri data).

Additional to beta estimates, t and p-values, we report 95% confidence intervals (CIs) calculated via the Wald method. All conducted tests were two-tailed and assessed at a significance level of 0.05.

1.1.2.4 Correlations between blood pressure and neural activity

As exploratory analyses and to investigate whether the *learning effect* during "neurofeedback with Stroop" – the change in the Stroop effect over trials (interaction Stroop*block) – was associated in the fMRI and blood pressure data, we calculated Pearson's product-moment correlation coefficients between the extracted learning effect values from individual mixed effects models. These were random-effects-only models, which enabled the extraction of individual parameters for each subject, and included the relevant interaction which was extracted (Stroop*trial) and the related two main effects, all as random effects over subjects. Similarly, for the "neurofeedback without Stroop" phase, we extracted the main effect of subphase from such mixed models. Outliers were removed for each individual correlation based on Cook's distance with a threshold of 4/n [35].

Table S1. Sample characteristics stratified by condition

Table 1: Sample description by condition

Categorical variables			
Variable	**Category**	***n (Control)***	***n (Experimental)***
Marital status	Single	9	13
	In a relationship	4	4
Highest degree	High school or equivalent	12	15
	Bachelors degree	1	2
Size of household (including participant)	1	0	2
	2	0	0
	3	1	0
	4	11	12
	5	0	3
"I am very experienced in using smartphones"	Strongly agree	4	4
	Agree	4	12
	Neutral	3	1
	Disagree	1	0
	Strongly disagree	1	0
Continuous variables			
Variable (unit)	**Statistic**	**Value (Control)**	**Value (Experimental)**
Age (years)	Mean	24.54	24.59
	SD	2.15	2.43
	Range [min, max]	[21, 28]	[20, 30]
Full time education (years)	Mean	15.31	14.94
	SD	1.32	1.43
	Range [min, max]	[13, 18]	[12, 18]

291 **Table S2.** fMRI one sample t-test results stroop activity in the functional localizer phase

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Table 4: fMRI one-sample t test results Stroop effect in functional localizer phase incongruent >congruent trials - all subjects

Cluster-level				Peak-level					Position (mm)			
p(FWE-corr)	**p(FDR-corr)**	**equivk**	**p(unc)**	**p(FWE-corr)**	**p(FDR-corr)**	**T**	**equivZ**	**p(unc)**	**x**	**y**	**z**	**AAL label**
Functional Localizer												
Incongruent >Congruent Stroop Trials												
<0.001	<0.001	1825	<0.001	<0.001	0.011	87.32	6.19	<0.001	12	-1	64	Supp_Motor_Area_R
				<0.001	0.011	86.79	6.18	<0.001	-36	-4	55	Precentral_L
				<0.001	0.043	68.01	5.76	<0.001	-21	-4	64	Frontal_Sup_L
<0.001	<0.001	690	<0.001	<0.001	0.043	70.18	5.81	<0.001	-24	-61	46	Parietal_Sup_L
				<0.001	0.058	60.38	5.55	<0.001	-33	-85	13	Occipital_Mid_L
				0.001	0.092	54.53	5.37	<0.001	-18	-70	52	Parietal_Sup_L
<0.001	<0.001	269	<0.001	<0.001	0.043	66.35	5.71	<0.001	18	-64	55	Parietal_Sup_R
				0.003	0.146	49.24	5.2	<0.001	33	-49	52	Parietal_Inf_R
				0.003	0.146	48.08	5.15	<0.001	24	-76	49	Parietal_Sup_R
<0.001	<0.001	120	<0.001	0.001	0.061	58.82	5.5	<0.001	27	26	-5	Insula_R
				0.003	0.146	48.09	5.15	<0.001	33	35	10	Insula_R
				0.013	0.334	39.77	4.83	<0.001	30	44	10	Frontal_Sup_R
<0.001	<0.001	98	<0.001	0.002	0.109	52.48	5.31	<0.001	39	-82	7	Occipital_Mid_R
				0.01	0.293	40.87	4.87	<0.001	54	-52	-5	Temporal_Inf_R
				0.018	0.43	37.7	4.74	<0.001	51	-64	-8	Temporal_Inf_R
<0.001	<0.001	131	<0.001	0.003	0.146	47.8	5.14	<0.001	48	14	28	Frontal_Inf_Oper_R
				0.03	0.614	35.05	4.61	<0.001	42	23	22	Frontal_Inf_Tri_R
<0.001	0.007	48	0.003	0.005	0.194	45.35	5.05	<0.001	21	-70	-50	Cerebelum_8_R
				0.005	0.196	44.72	5.03	<0.001	9	-70	-47	Cerebelum_8_R
				0.019	0.442	37.46	4.73	<0.001	0	-70	-38	Vermis_8
				0.016	0.397	38.46	4.77	<0.001	57	-64	34	Angular_R
<0.001	0.006	52	0.002	0.007	0.211	43.48	4.98	<0.001	-36	-37	43	Parietal_Inf_L
0.001	0.047	24	0.028	0.007	0.217	43.15	4.97	<0.001	-60	-16	25	Postcentral_L
0.001	0.043	26	0.023	0.015	0.381	38.92	4.79	<0.001	27	-67	-23	Cerebelum_6_R

Reported are only clusters with a minimal size of k = 20 voxels. For the complete list of all clusters, see Tables XXXXX in Appendix//Supplement. Tresholded for voxel-wise FWE-correction p<0.05 (wholebrain). Height threshold: T = 5.15, p = 0.000 (0.050); Extent threshold: k = 0 voxels; Expected voxels per cluster, ¡k¿ = 12.264; Expected number of clusters, ¡c¿ = 0.05; FWEp: 5.154, FDRp: 7.586, FWEc: 3, FDRc: 78; Degrees of freedom = [1.0, 28.0]; FWHM = 23.0 23.4 23.8 mm mm mm; 7.7 7.8 7.9 voxels; Volume: 1617759 = 59917 voxels = 113.2 resels; Voxel size: 3.0 3.0 3.0 mm mm mm; (resel = 475.54 voxels)

293 **Table S3.** fMRI one sample t-test results stroop activity in the "neurofeedback with
294 Stroop" phase

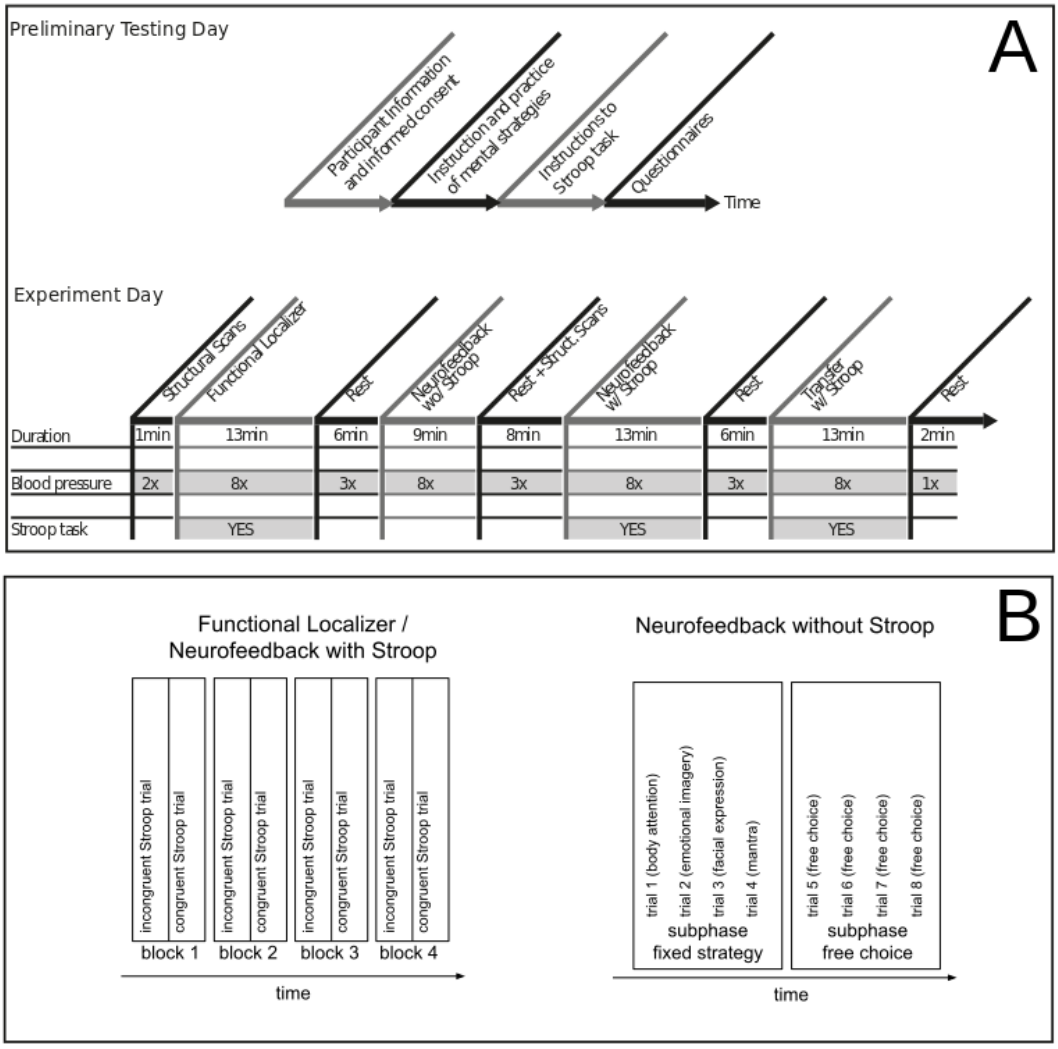
Table 5: fMRI one-sample t test results Stroop effect in phase "neurofeedback with stroop" incongruent >congruent trials – all subjects

Cluster-level				Peak-level				Position (mm)			
p(FWE-corr)	p(FDR-corr)	equivk	p(unc)	p(FWE-corr)	p(FDR-corr)	T	equivZ	p(unc)	x	y	z	AAL label
Neurofeedback with Stroop												
Incongruent >Congruent Stroop Trials												
<0.001	0.01	113	0.003	<0.001	0.006	76.92	5.97	<0.001	51	-67	43	Angular_R
				0.012	0.302	36.58	4.69	<0.001	63	-49	37	Angular_R
<0.001	0.01	104	0.004	<0.001	0.011	66.43	5.72	<0.001	-48	-73	40	Occipital_Mid_L
				<0.001	0.018	59.06	5.51	<0.001	-57	-64	31	Angular_L
				0.003	0.093	44.82	5.03	<0.001	-57	-58	43	Angular_L
<0.001	0.01	131	0.001	<0.001	0.012	63.57	5.64	<0.001	-45	11	28	Frontal_Inf_Oper_L
<0.001	0.013	82	0.008	0.001	0.038	52.82	5.32	<0.001	-27	-94	-2	Occipital_Mid_L
<0.001	0.013	89	0.006	0.002	0.073	47.79	5.14	<0.001	-36	-46	46	Parietal_Inf_L
				0.009	0.24	38.28	4.76	<0.001	-24	-64	43	Parietal_Sup_L
0.001	0.03	58	0.022	0.002	0.085	46.02	5.08	<0.001	27	-94	1	Occipital_Mid_R
0.039	0.776	1	0.776	0.033	0.712	31.4	4.43	<0.001	-33	-4	58	Precentral_L
0.03	0.675	3	0.591	0.04	0.79	30.55	4.38	<0.001	-12	-67	58	Precuneus_L

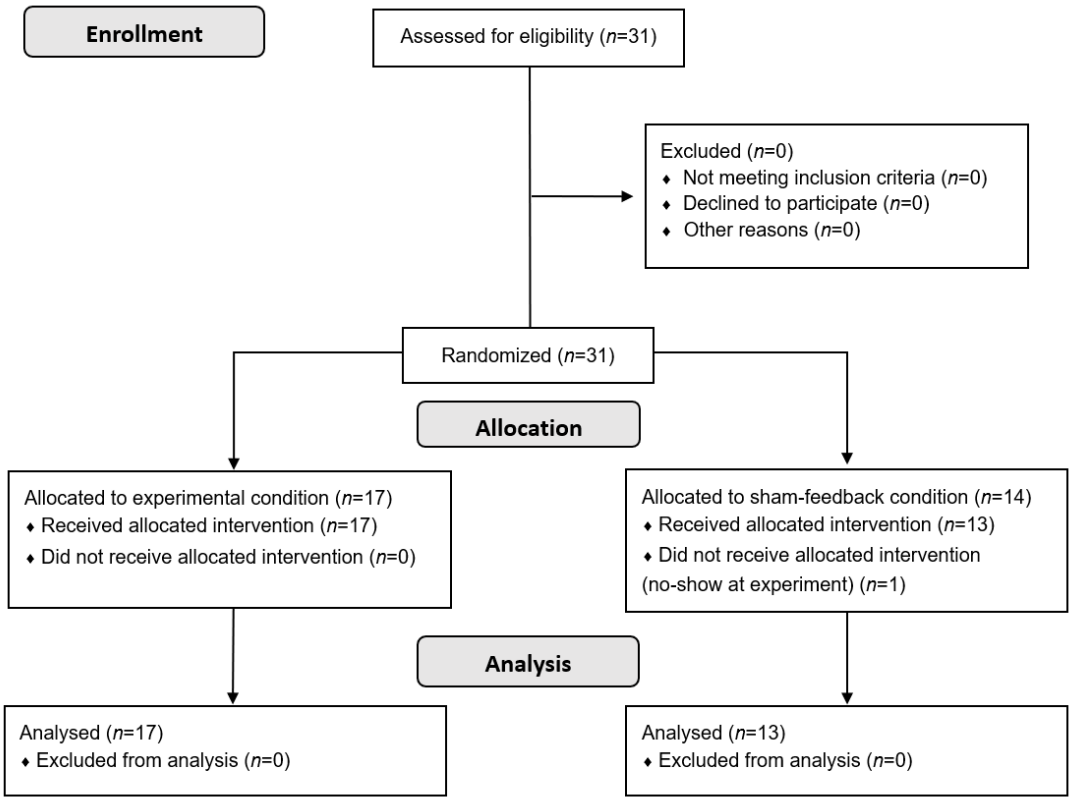
Reported are only clusters with a minimal size of k = 20 voxels. For the complete list of all clusters, see Tables XXXXX in Appendix//Supplement. Height threshold: T = 5.15, p = 0.000 (0.050); Extent threshold: k = 0 voxels; Expected voxels per cluster, ¡k¿ = 12.264; Expected number of clusters, ¡c¿ = 0.05; FWEp: 5.154, FDRp: 7.586, FWEc: 3, FDRc: 78; Degrees of freedom = [1.0, 28.0]; FWHM = 23.0 23.4 23.8 mm mm mm; 7.7 7.8 7.9 voxels; Volume: 1617759 = 59917 voxels = 113.2 resels; Voxel size: 3.0 3.0 3.0 mm mm mm; (resel = 475.54 voxels)

295

Figure S4. Study and experiment procedures



298 **Table S5.** Participant flow through study



299
300

Figure S6. Stroop task related fMRI activity

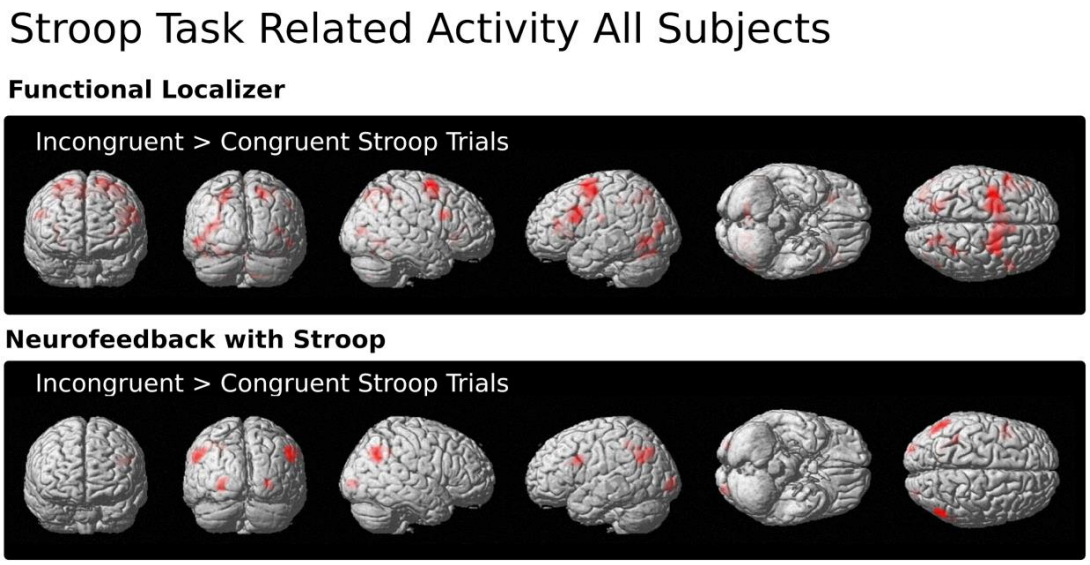


Figure S7. Correlations blood pressure and fMRI learning effects

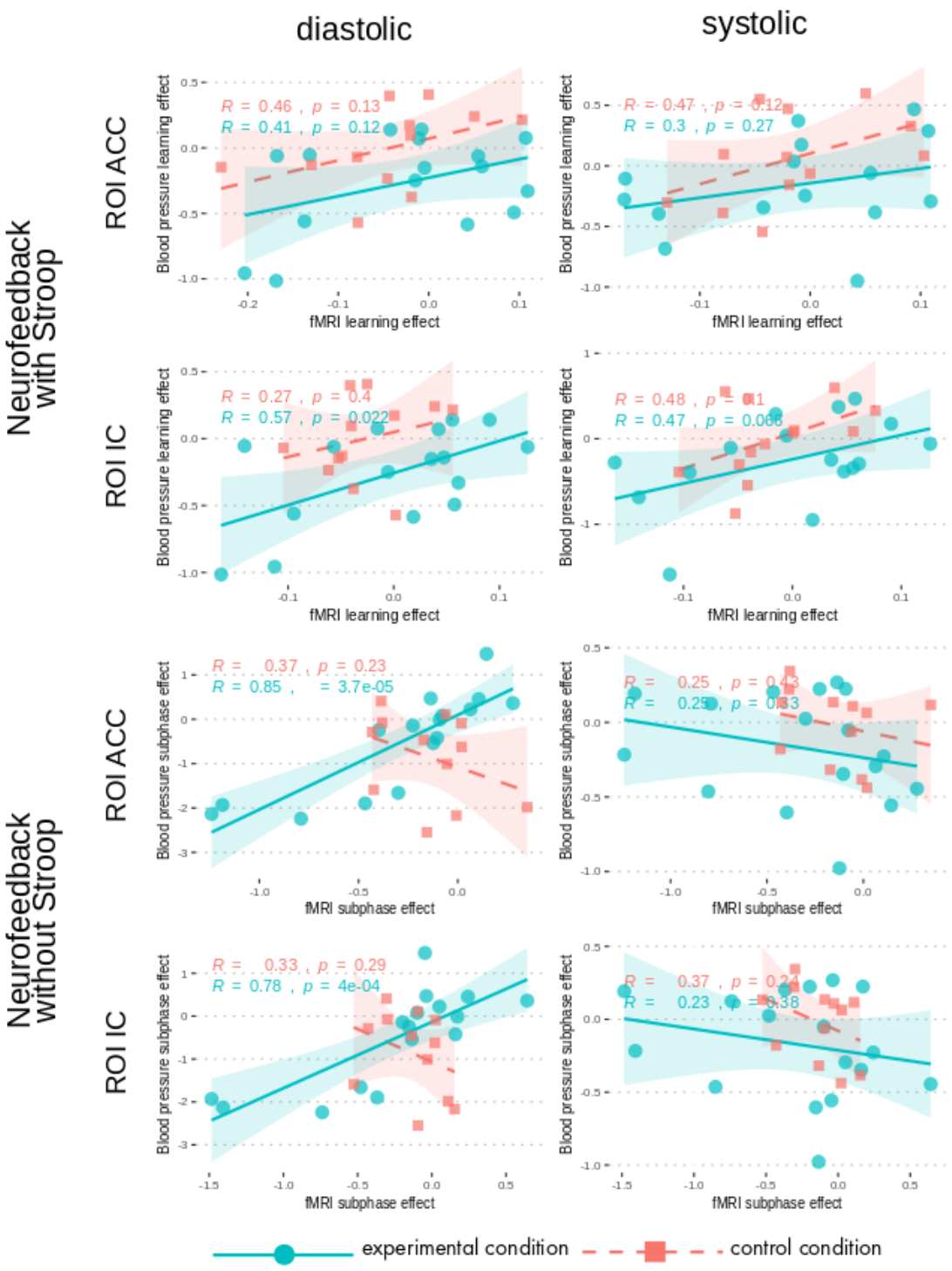


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Table S1. Sample characteristics stratified by condition

Categorical variables			
Variable	***Category***	***n control***	***n experimental***
Marital status	Single	9	13
	In a relationship	4	4
Highest degree	High school or equivalent	12	15
	Bachelor's degree	1	2
Size of household (including participant)	1	0	2
	2	0	0
	3	1	0
	4	11	12
	5	0	3
"I am very experienced in using smartphones"	Strongly agree	4	4
	Agree	4	12
	Neutral	3	1
	Disagree	1	0
	Strongly disagree	1	0

Continuous variabes			
Variable (unit)	***Value***	***control***	***experimental***
Age (years)	Mean	24.54	24.59
	SD	2.15	2.43
	Range [min, max]	[21, 28]	[20, 30]
Full time education (years)	Mean	15.31	14.94
	SD	1.32	1.43
	Range [min, max]	[13, 18]	[12, 18]

Table S2. fMRI one-sample t-test results Stroop effect in functional localizer phase

Contrast: Incongruent > Congruent Stroop Trials

Cluster-level				Peak-level					Position (in mm)			
p(FWE-corr)	***p(FDR-corr)***	***equivk***	***p(unc)***	***p(FWE-corr)***	***p(FDR-corr)***	***F***	***equivZ***	***p(unc)***	***x***	***y***	***z***	***AAL Label***
0	0	1825	0	0	0,011	87,32	6,19	0	12	-1	64	Supp_Motor_Area_R
				0	0,011	86,79	6,18	0	-36	-4	55	Precentral_L
				0	0,043	68,01	5,76	0	-21	-4	64	Frontal_Sup_L
0	0	690	0	0	0,043	70,18	5,81	0	-24	-61	46	Parietal_Sup_L
				0	0,058	60,38	5,55	0	-33	-85	13	Occipital_Mid_L
				0,001	0,092	54,53	5,37	0	-18	-70	52	Parietal_Sup_L
0	0	269	0	0	0,043	66,35	5,71	0	18	-64	55	Parietal_Sup_R
				0,003	0,146	49,24	5,2	0	33	-49	52	Parietal_Inf_R
				0,003	0,146	48,08	5,15	0	24	-76	49	Parietal_Sup_R
0	0	120	0	0,001	0,061	58,82	5,5	0	27	26	-5	Insula_R
				0,003	0,146	48,09	5,15	0	33	35	10	Insula_R
				0,013	0,334	39,77	4,83	0	30	44	10	Frontal_Sup_R
0	0	98	0	0,002	0,109	52,48	5,31	0	39	-82	7	Occipital_Mid_R
				0,01	0,293	40,87	4,87	0	54	-52	-5	Temporal_Inf_R
				0,018	0,43	37,7	4,74	0	51	-64	-8	Temporal_Inf_R
0	0	131	0	0,003	0,146	47,8	5,14	0	48	14	28	Frontal_Inf_Oper_R
				0,03	0,614	35,05	4,61	0	42	23	22	Frontal_Inf_Tri_R
0	0,007	48	0,003	0,005	0,194	45,35	5,05	0	21	-70	-50	Cerebelum_8_R
				0,005	0,196	44,72	5,03	0	9	-70	-47	Cerebelum_8_R
				0,019	0,442	37,46	4,73	0	0	-70	-38	Vermis_8
0,004	0,103	15	0,073	0,005	0,194	44,98	5,04	0	-3	-76	-14	Vermis_6
0,005	0,137	12	0,105	0,006	0,203	43,95	5	0	51	-67	43	Angular_R
				0,016	0,397	38,46	4,77	0	57	-64	34	Angular_R
0	0,006	52	0,002	0,007	0,211	43,48	4,98	0	-36	-37	43	Parietal_Inf_L
0,001	0,047	24	0,028	0,007	0,217	43,15	4,97	0	-60	-16	25	Postcentral_L
0,017	0,359	4	0,338	0,009	0,254	41,96	4,92	0	27	50	-11	Frontal_Mid_Orb_R
0,001	0,043	26	0,023	0,015	0,381	38,92	4,79	0	27	-67	-23	Cerebelum_6_R
0,009	0,217	8	0,178	0,017	0,42	38,05	4,75	0	-21	-67	-50	Cerebelum_8_L
0,003	0,1	16	0,065	0,018	0,424	37,89	4,75	0	48	-46	-20	Temporal_Inf_R
0,014	0,322	5	0,284	0,024	0,528	36,21	4,67	0	3	-82	-26	Cerebelum_Crus2_R
0,033	0,65	1	0,65	0,042	0,845	33,24	4,52	0	-12	20	34	Cingulum_Mid_L

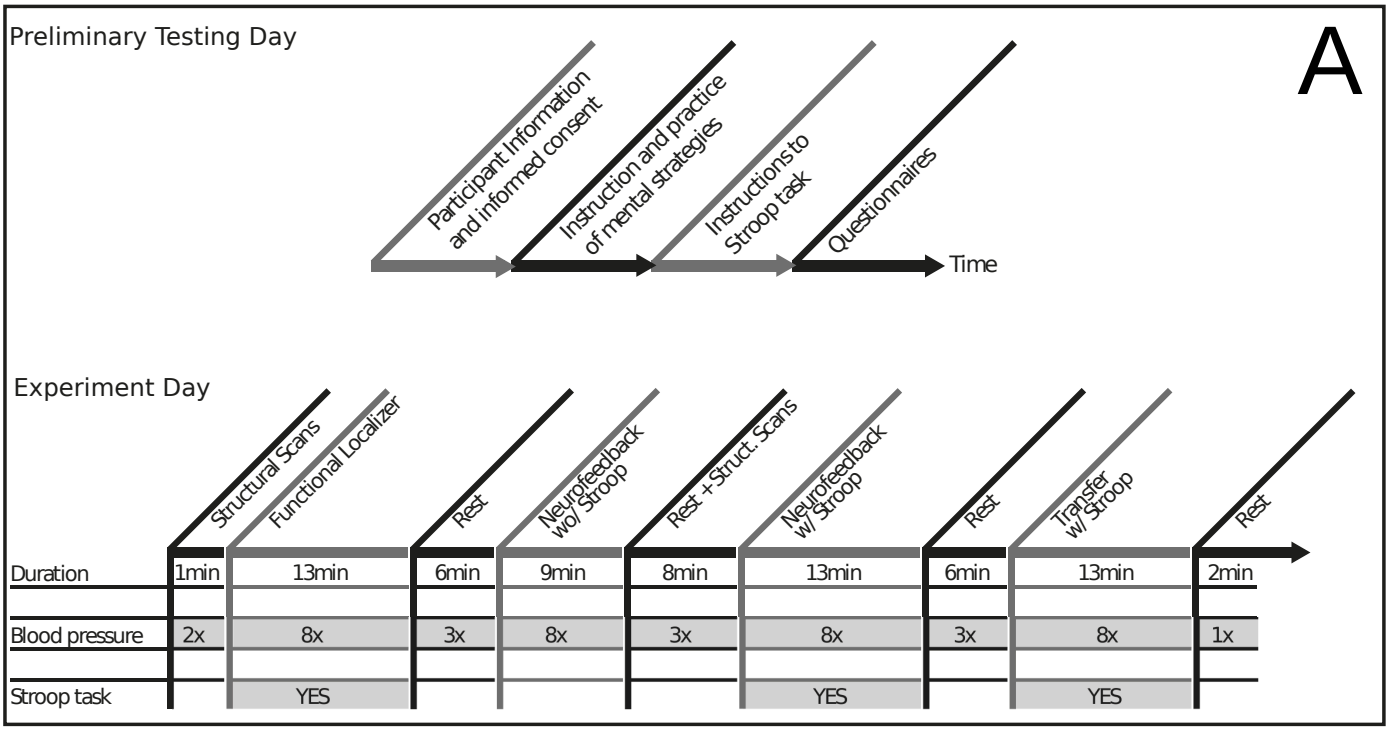
Tresholded for voxel-wise FWE-correction p < 0.05 (wholebrain). Height threshold: T = 5.15, p = 0.000 (0.050); Extent threshold: k = 0 voxels; Expected voxels per cluster, <k> = 12.264; Expected number of clusters, <c> = 0.05; FWEp: 5.154, FDRp: 7.586, FWEc: 3, FDRc: 78; Degrees of freedom = [1.0, 28.0]; FWHM = 23.0 23.4 23.8 mm mm mm; 7.7 7.8 7.9 {voxels}; Volume: 1617759 = 59917 voxels = 113.2 resels; Voxel size: 3.0 3.0 3.0 mm mm mm; (resel = 475.54 voxels)

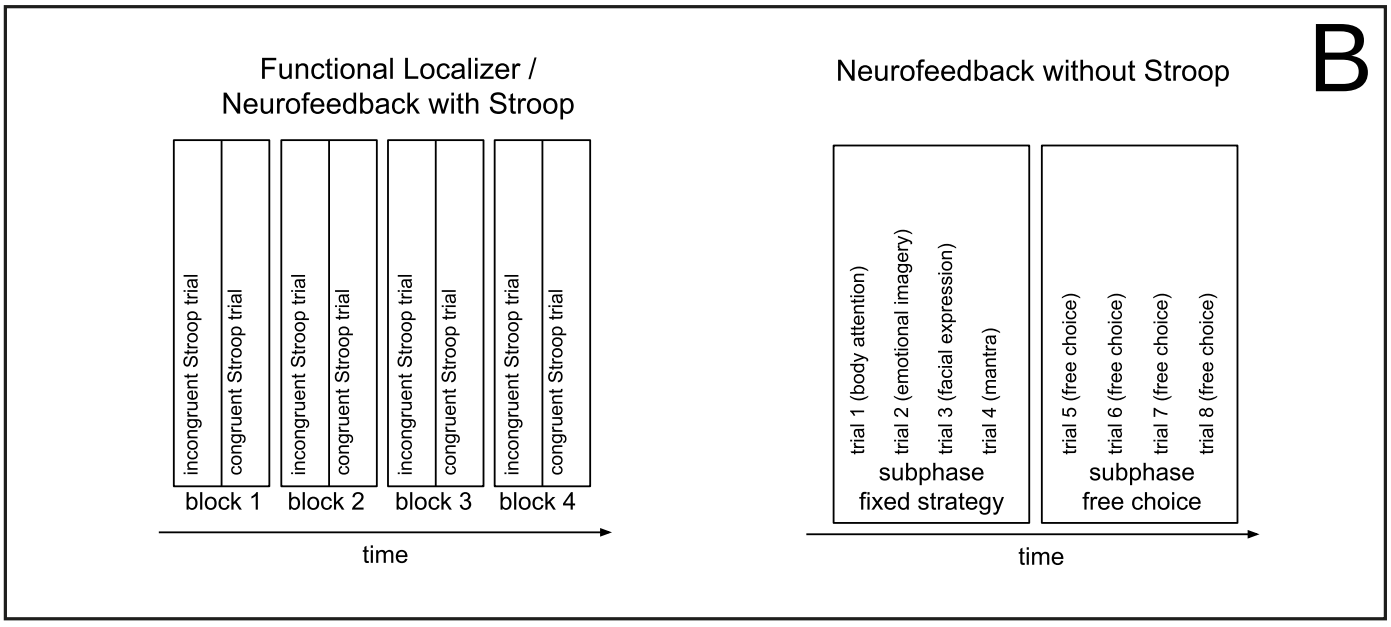
Table S3. fMRI one-sample t-test results Stroop effect in phase "Neurofeedback with Stroop"

Contrast: Incongruent > Congruent Stroop Trials

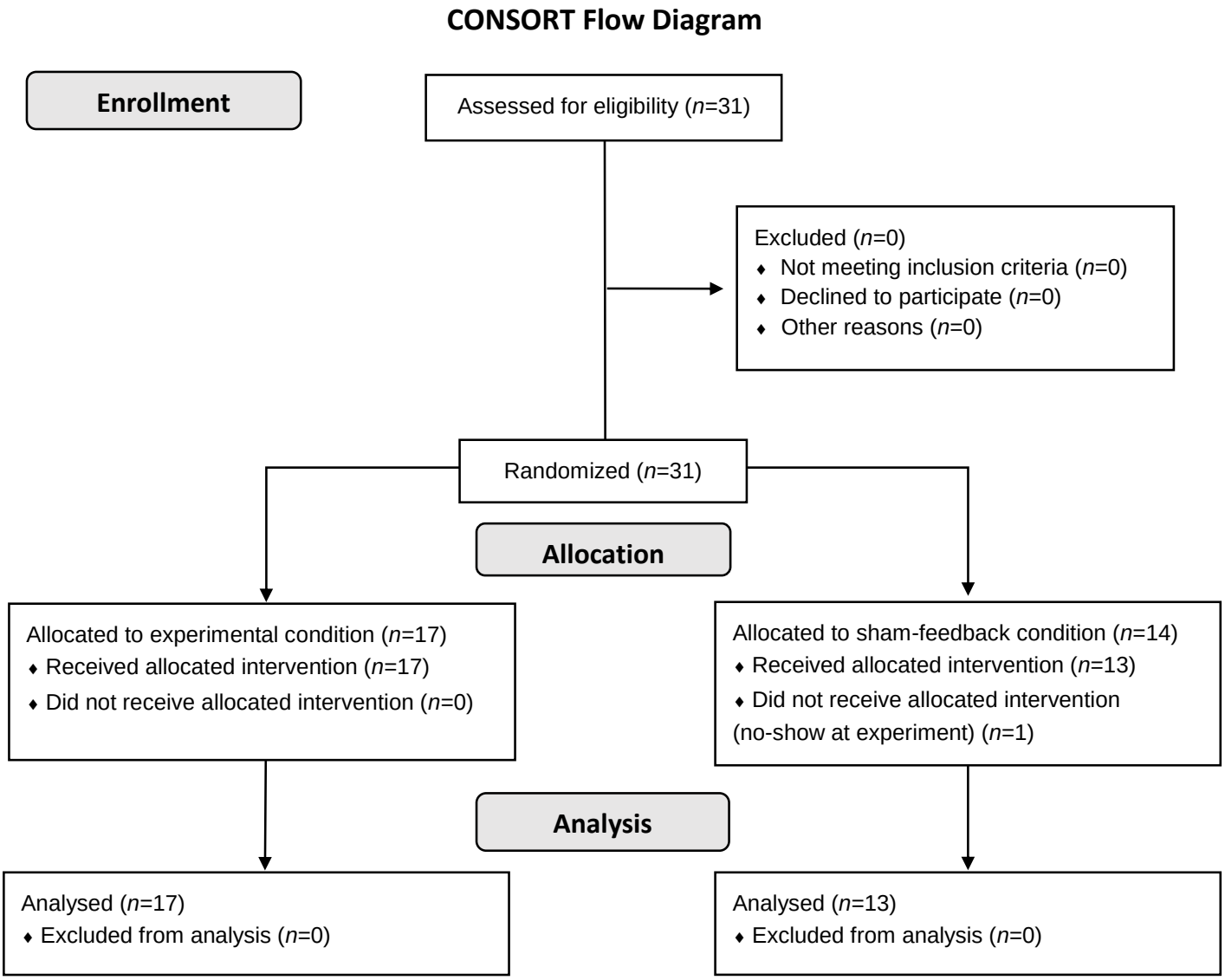
Cluster-level				Peak-level					Position (in mm)			
p(FWE-corr)	***p(FDR-corr)***	***equivk***	***p(unc)***	***p(FWE-corr)***	***p(FDR-corr)***	***F***	***equivZ***	***p(unc)***	***x***	***y***	***z***	***AAL Label***
0	0,01	113	0,003	0	0,006	76,92	5,97	0	51	-67	43	Angular_R
				0,012	0,302	36,58	4,69	0	63	-49	37	Angular_R
0	0,01	104	0,004	0	0,011	66,43	5,72	0	-48	-73	40	Occipital_Mid_L
				0	0,018	59,06	5,51	0	-57	-64	31	Angular_L
				0,003	0,093	44,82	5,03	0	-57	-58	43	Angular_L
0	0,01	131	0,001	0	0,012	63,57	5,64	0	-45	11	28	Frontal_Inf_Oper_L
0	0,013	82	0,008	0,001	0,038	52,82	5,32	0	-27	-94	-2	Occipital_Mid_L
0	0,013	89	0,006	0,002	0,073	47,79	5,14	0	-36	-46	46	Parietal_Inf_L
				0,009	0,24	38,28	4,76	0	-24	-64	43	Parietal_Sup_L
0,001	0,03	58	0,022	0,002	0,085	46,02	5,08	0	27	-94	1	Occipital_Mid_R
0,039	0,776	1	0,776	0,033	0,712	31,4	4,43	0	-33	-4	58	Precentral_L
0,03	0,675	3	0,591	0,04	0,79	30,55	4,38	0	-12	-67	58	Precuneus_L

Tresholded for voxel-wise FWE-correction p < 0.05 (wholebrain). Height threshold: T = 5.15, p = 0.000 (0.050); Extent threshold: k = 0 voxels; Expected voxels per cluster, <k> = 12.264; Expected number of clusters, <c> = 0.05; FWEp: 5.154, FDRp: 7.586, FWEc: 3, FDRc: 78; Degrees of freedom = [1.0, 28.0]; FWHM = 23.0 23.4 23.8 mm mm mm; 7.7 7.8 7.9 {voxels}; Volume: 1617759 = 59917 voxels = 113.2 resels; Voxel size: 3.0 3.0 3.0 mm mm mm; (resel = 475.54 voxels)


A
Preliminary Testing Day
Participant Information and informed consent
Instruction and practice of mental strategies
Instructions to Stroop task
Questionnaires
Time
Experiment Day
Structural Scans
Functional Localizer
Rest
Neurofeedback w/o Stroop
Rest + Struct. Scans
Neurofeedback w/ Stroop
Rest
Transfer w/ Stroop
Rest
Duration
1min
13min
6min
9min
8min
13min
6min
13min
2min
Blood pressure
2x
8x
3x
8x
3x
8x
3x
8x
1x
Stroop task
YES
YES
YES

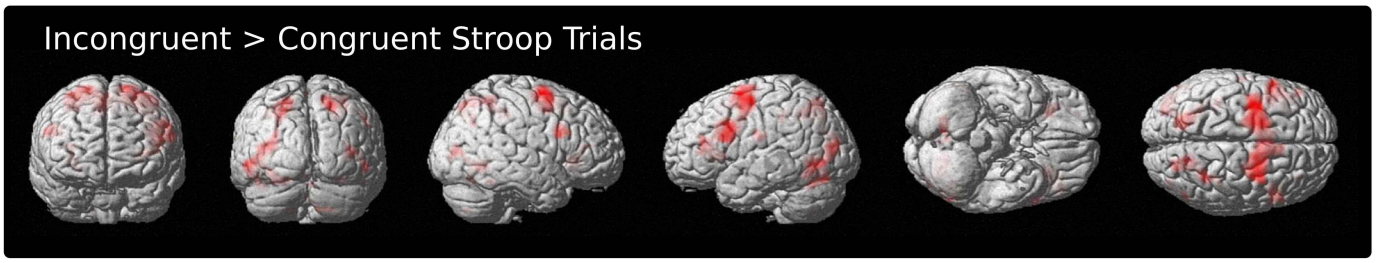

B
Functional Localizer / Neurofeedback with Stroop
incongruent Stroop trial
congruent Stroop trial
block 1
block 2
block 3
block 4
time
Neurofeedback without Stroop
trial 1 (body attention)
trial 2 (emotional imagery)
trial 3 (facial expression)
trial 4 (mantra)
subphase fixed strategy
trial 5 (free choice)
trial 6 (free choice)
trial 7 (free choice)
trial 8 (free choice)
subphase free choice
time

CONSORT flow diagram for the publication “Real-time fMRI Neurofeedback to Modulate Neural and Cardiovascular Stress Response: A Randomized Controlled Trial”

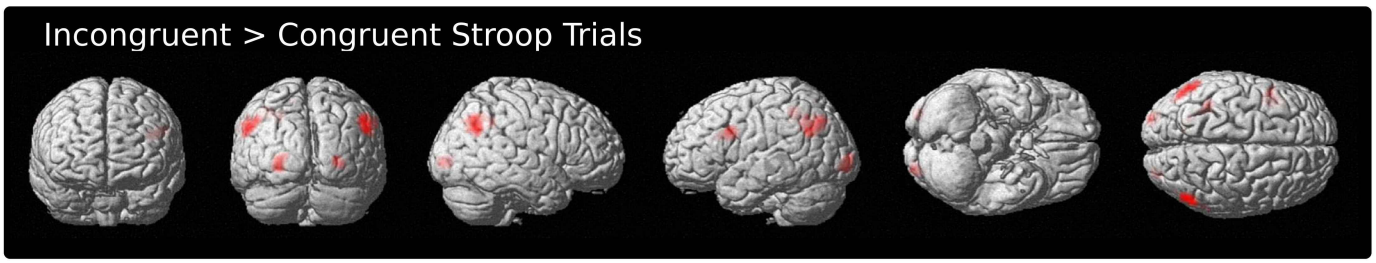


Stroop Task Related Activity All Subjects

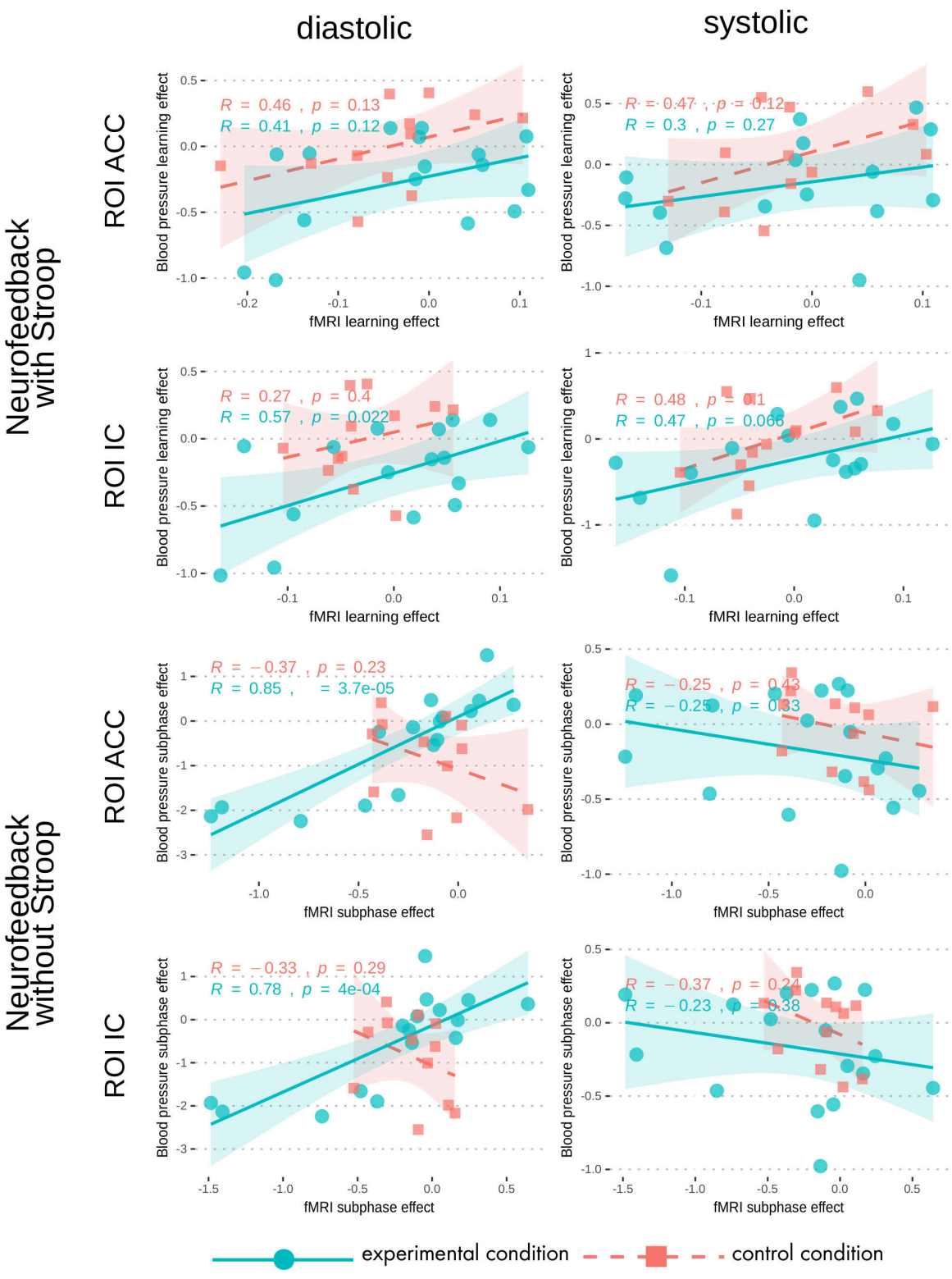
Functional Localizer



Neurofeedback with Stroop



Individual one-sample t-tests for whole sample (n=30)
P<0.05 FWE-corrected


diastolic
systolic
Neurofeedback with Stroop
Neurofeedback without Stroop
ROI ACC
ROI IC
ROI ACC
ROI IC
Blood pressure learning effect
fMRI learning effect
Blood pressure subphase effect
fMRI subphase effect
R = 0.46 , p = 0.13
R = 0.41 , p = 0.12
R = 0.47 , p = 0.12
R = 0.3 , p = 0.27
R = 0.27 , p = 0.4
R = 0.57 , p = 0.022
R = 0.48 , p = 0.1
R = 0.47 , p = 0.066
R = −0.37 , p = 0.23
R = 0.85 , = 3.7e-05
R = −0.25 , p = 0.43
R = −0.25 , p = 0.33
R = −0.33 , p = 0.29
R = 0.78 , p = 4e-04
R = −0.37 , p = 0.24
R = −0.23 , p = 0.38
experimental condition
control condition

CONSORT checklist for the publication "Real-time fMRI Neurofeedback to Modulate Neural and Cardiovascular Stress Response: A Randomized Controlled Trial"

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	Title
	1b	Structured summary of trial design, methods, results, and conclusions	Abstract
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	Introduction main text
	2b	Specific objectives or hypotheses	Introduction last paragraph p. 3
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	Main manuscript: Overall study procedure p. 4
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	-----
Participants	4a	Eligibility criteria for participants	Main manuscript: Participants p. 3
	4b	Settings and locations where the data were collected	Main manuscript: Participants p. 3
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	Main manuscript: Participants p. 3; Randomization and blinding p. 6; neurofeedback protocol and feedback presentation p.6; Mental Strategies p.6; Supplement: Mental strategies p. 5; Neurofeedback protocol and feedback presentation p. 5; Online data processing and feedback signal calculation p. 6
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	Main manuscript: Outcomes and instruments p. 5
	6b	Any changes to trial outcomes after the trial commenced, with reasons	-----
Sample size	7a	How sample size was determined	Supplement: Participants p. 2

	7b	When applicable, explanation of any interim analyses and stopping guidelines	-----
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	Supplement: Randomization and blinding p. 4
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	Supplement: Randomization and blinding p. 4
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	Supplement: Randomization and blinding p. 4
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	Supplement: Randomization and blinding p. 4
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	Main manuscript: Randomization and blinding p.6; Supplement: Randomization and blinding p. 4
	11b	If relevant, description of the similarity of interventions	Main manuscript: Randomization and blinding p.6
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	Main manuscript: Linear mixed effects models for fMRI and blood pressure, p. 7
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	Main manuscript: Correlations between blood pressure and neuronal activity p. 8
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	Sample description and participant flow p. 8
	13b	For each group, losses and exclusions after randomisation, together with reasons	Sample description and participant flow p. 8
Recruitment	14a	Dates defining the periods of recruitment and follow-up	Sample description and participant flow p. 8
	14b	Why the trial ended or was stopped	Supplement: Participants, p. 2
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Supplement Table S1
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	Sample description and participant flow p. 8; Supplement Figure S5

			(Participant Flow)
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	Tables 1 and 2 and Figures 1 and 2; Adverse events during neurofeedback training, p. 10
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	-----
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	Stressor-evoked fMRI activity, p. 8; Correlation between fMRI activity and blood pressure, p. 9
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	Adverse events during neurofeedback training, p. 10
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	Discussion, p. 10-12
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	Discussion, p. 12
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	Discussion, p. 10-12
Other information			
Registration	23	Registration number and name of trial registry	Abstract; Overall study procedure, p. 4
Protocol	24	Where the full trial protocol can be accessed, if available	-----
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	Funding sources, p. 13

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

2.2 Publication 2: Does fMRI neurofeedback in the context of stress influence mood and arousal? A randomised controlled trial with parallel group design

Full reference: A. Belardi, J.-H. Lee, H.-C. Kim, E. Stalujanis, E. K. Jung, M. Oh, S.-S. Yoo, J. C. Pruessner, M. Tegethoff, and G. Meinlschmidt. Does fMRI Neurofeedback in the Context of Stress Influence Mood and Arousal? A Randomised Controlled Trial with Parallel Group Design [version 2; peer review: 1 approved]. *F1000Research*, 8:1031, 2019. ISSN 2046-1402. doi:10.12688/f1000research.19403.2

RESEARCH ARTICLE

REVISED Does fMRI neurofeedback in the context of stress influence mood and arousal? A randomised controlled trial with parallel group design [version 2; peer review: 1 approved]

Angelo Belardi [1], Jong-Hwan Lee[2], Hyun-Chul Kim[2], Esther Stalujanis[1,3], Eun Kyung Jung[2], Minkyung Oh[2], Seung-Schik Yoo[4], Jens C. Pruessner[5], Marion Tegethoff[1*], Gunther Meinlschmidt [3,6,7*]

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Latest published: 28 Nov 2019, **8**:1031 (https://doi.org/10.12688/f1000research.19403.2)

Abstract

Background: Stress-related mental and physical health issues burden modern societies. New treatment opportunities could help to lessen long-term detrimental consequences of stress.
Objective: To investigate whether real-time functional magnetic resonance imaging neurofeedback (rtfMRInf), aimed at modulating brain activity associated with a stressor, affects subjective mood and arousal.
Methods: In total, 30 males participated in a randomised controlled trial with parallel-group design. rtfMRInf was the intervention, sham-neurofeedback the control condition, and the Stroop task the stressor. We instructed participants to modulate their stress response to the Stroop task via feedback from their anterior cingulate cortex and their insular cortex, concomitantly applying mental strategies. We assessed mood with the Multidimensional Mood State Questionnaire (dimensions: good/bad, GB; awake/tired, AT; and calm/nervous, CN), and subjective arousal with Self-Assessment Manikins (SAM).
Results: We found significantly higher subjective arousal after neurofeedback phases in the experimental condition as compared to the control condition [t(26.6) = –2.216, 95%CI [–2.188,–0.083], p = 0.035; t(27.9) = –3.252, 95%CI [–2.685,–0.609], p = 0.003], but no significant differences between the conditions regarding mood [GB: b = 0.4, 95%CI [–0.67, 1.47], p = 0.467; AT: b = 0.769, 95%CI [–0.319, 1.857], p = 0.177; CN: b = 0.5, 95%CI [–0.53, 1.53], p = 0.352]. In both conditions, there was significantly worse and more tired mood after the fMRI session as

Open Peer Review

Reviewer Status ✔

	Invited Reviewers
	1
REVISED **version 2** published 28 Nov 2019	
version 1 published 09 Jul 2019	✔ report

1 **Ryuichiro Hashimoto**, Showa University, Tokyo, Japan
Tokyo Metropolitan University, Hachioji, Japan

Any reports and responses or comments on the article can be found at the end of the article.

compared to before [GB:b = –0.77, 95% CI [–1.31, 0.23], p = 0.009; AT: b = –0.652, 95%CI [–1.116,–0.187], p = 0.01].
Conclusions: Findings indicate that rtfMRInf led to higher arousal, which may counteract the aim to reduce stress responses. Whether the multitasking situation has triggered this neurofeedback-related arousal – and how to circumvent it – asks for further study.
Trial registration: NCT01921088, ClinicalTrials.gov, 13th August 2013.

Keywords
arousal, dual task, multitasking, functional magnetic resonance imaging, mood, neurofeedback, psychological stress

Corresponding authors: Marion Tegethoff (marion.tegethoff@unibas.ch), Gunther Meinlschmidt (gunther.meinlschmidt@unibas.ch)

Author roles: Belardi A: Data Curation, Formal Analysis, Methodology, Software, Visualization, Writing – Original Draft Preparation, Writing – Review & Editing; **Lee JH**: Conceptualization, Data Curation, Investigation, Methodology, Project Administration, Resources, Software, Supervision, Writing – Review & Editing; **Kim HC**: Investigation, Software, Writing – Review & Editing; **Stalujanis E**: Data Curation, Writing – Review & Editing; **Jung EK**: Investigation, Software, Writing – Review & Editing; **Oh M**: Data Curation, Investigation, Writing – Review & Editing; **Yoo SS**: Conceptualization, Methodology, Resources, Writing – Review & Editing; **Pruessner JC**: Conceptualization, Methodology, Writing – Review & Editing; **Tegethoff M**: Conceptualization, Data Curation, Funding Acquisition, Methodology, Project Administration, Resources, Supervision, Writing – Review & Editing; **Meinlschmidt G**: Conceptualization, Data Curation, Methodology, Project Administration, Resources, Supervision, Writing – Review & Editing

Competing interests: No competing interests were disclosed.

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The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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First published: 09 Jul 2019, **8**:1031 (https://doi.org/10.12688/f1000research.19403.1)

REVISED **Amendments from Version 1**

Based on reviewer comments, we added information to the methods section about the definition of the anatomical ROIs and included more details to clarify the calculation of individual functional ROIs. In the discussion section, we added further ideas for future investigations and the limitation of using English questionnaires with Korean participants.

Any further responses from the reviewers can be found at the end of the article

Introduction

Stress is ubiquitous in life. Getting rid of it is neither realistic nor desirable, as Hans Selye pointed out: "complete freedom from stress is death!"[1, p. 137]. However, accepting stress as part of our lives does not mean we are all heading towards long-term detrimental consequences of this inevitability. We can influence how a stressor affects us in the long run. For this, let us begin with how we react to a stressor: The stress response is manifested in physiological and psychological aspects and leads to specific behavior. Physiologically, stress for example increases blood pressure, heart rate, and specific brain activity, and triggers a cascade of endocrine activity which ends in glucocorticoid release[2,3]. Psychologically, stress leads to focused attention and increased arousal and alertness, and shows up in behavioral measures such as self-reported questionnaires[2].

This response ensures survival in the presence of a life-threatening stressor, or at least increases the chance of survival. In everyday life in a modern society, however, the response might overshoot, given the nature of the stressors we are facing. And accumulated or chronic stress can lead to dire mental and physical health issues: Stress-related mental disorders like depression and anxiety, which are globally a main source of adult disability[4] for example, or hypertension[5], which is the top modifiable risk factor for mortality[6].

The effects of stress and related disorders burden industrialized countries increasingly. Associated costs have been estimated to 20 billion euros per year, in the European Union alone[7]. It is also a topic which affects most of us eventually: 49% of people in a survey in the United States had a major stressful event in a one year time-window[8]. When asked how often they experience stress in their daily life, 44% of respondents said "frequently" and 35% "sometimes" to a Gallup poll conducted in the US in 2017[9].

Finding ways to better deal with stressors in the short term might spare us of these long-term consequences and lessen the burden on the individual and society. In the definition of psychological stress by Lazarus and Folkman, our own appraisal of a situation and our coping abilities take a major role: "a relationship with the environment that the person appraises as significant for his or her well-being and in which the demands tax or exceed available coping resources"[10, p. 63].

Cognitive and behavioral techniques used in occupation-specific stress management programs are also known to psychotherapeutic practice. Intervention programs for stress management often include education about and practice of time-management and coping skills, psychoeducation, relaxation techniques (e.g. Jacobson's progressive muscle relaxation, controlled breathing, hypnosis), mindfulness-based stress reduction, exercise, leveraging social support, or training in specific job-related skills to prevent or prepare for common stressors[11–14]. Yoga and meditation-based therapies have both also been associated with mood changes in people with the stress-related disorders depression and anxiety[15]. The mechanism behind these changes might act via the biological stress system[16].

However, while there is support for classical stress management interventions[17], as with any treatment it is likely that a proportion of affected people do not respond to a given intervention. In such cases, innovative neuroscientifically-informed interventions might help. Such interventions are based on neuroscientific knowledge about the stress response and can be coupled with personal neural activity in reaction to a stressor. Due to that, they are likely to help participants work deliberately on their individual stress response.

Gaining deliberate control over specific and individual brain activity (and thus indirectly over mental processes) is a key aim of *neurofeedback*, an approach that has over the last decades been applied to modulate a wide set of mental processes and to improve symptoms to specific mental disorders[18]. Neurofeedback describes the paradigm to feed back a signal reflecting a person's own brain activity so that the person can use information contained in the signal to better modulate their brain activity[18]. An advantage of fMRI is that it allows to work with a spatially circumscribed region of the brain. Thus, one can use this approach to target various brain areas associated with different mental processes, in real-time functional magnetic resonance imaging neurofeedback (rtfMRInf). rtfMRInf has been applied to modulate diverse mental processes, including pain[19], anxiety[20], mood[21], and many others[22]. Whether the procedure could also be used to modulate the central and peripheral stress response has to the best of our knowledge not yet been investigated.

Within a larger rtfMRInf study, we assessed self-reported mood and arousal measures and tested whether these differed between the participants who had received real feedback from their own brain's activity, as compared to those who received sham feedback (the recorded brain activity of another participant). Participants thereby used one out of four different mental strategies (body attention, emotional imagery, facial expression, and contemplative repetition) to help them reduce their stress response. Details about these are available in our earlier publication[23]. The use of these strategies has shown to improve mood when trained once a day for 13 consecutive days, using smartphone-based instructions[23]. Here, we aimed to elucidate whether rtfMRInf aiming at modulating the central and peripheral stress response is related to changes in mood and subjective arousal. While we addressed the primary and secondary outcomes of the study, namely physiological components of stress (brain activity and blood pressure) and adverse events, in another manuscript (Belardi, Lee, Kim, Stalujanis, Jung, Oh,

Yoo, Pruessner, Tegethoff, Meinlschmidt; unpublished study), here we focus on additional outcomes, namely self-reported psychological measures of mood and arousal.

We assumed that effects of rtfMRInf on mood and arousal may show up in one of two potential directions: Neurofeedback may lead to i) improved mood and lower arousal (in line with its aim to reduce the stress response); or ii) worse mood and higher arousal (in line with increased mental workload based on the multitasking situation going along with rtfMRInf). The second direction might be due to our experiment requiring the participants to multitask: at the same time monitoring the feedback signal; applying a specific mental strategy; and conducting the Stroop task. Current research in the field of multitasking generally reports lower task performance when the task is performed in a multitasking setting, as compared to when it is done as a single task[24] and higher arousal for complex and multitasking situations[25,26].

Methods

Participants

We recruited 31 subjects and analyzed data of 30 of these (with mood and arousal data lacking from one subject, due to no-show for the main experiment). They were all male students at Korea University, Seoul, Republic of Korea. We allocated 17 of them to the experimental condition and 13 to the control condition, based on a predefined block-randomized scheme (blocks of 8, 10, and 12 with random order). The mean age was 24.6 years (SD=2.1) and 24.5 years (SD=2.4) in the experimental and the control condition, respectively with a mean of education of 14.9 years (SD=1.4) and 15.3 years (1.3), respectively. There were no significant differences between the conditions for these baseline characteristics [age: $t(28) = -0.0585$, $p = 0.954$; education years: $t(28) = 0.718$, $p = 0.479$].

We based the sample size on previous studies which had shown large effect sizes for rtfMRInf[19,27]. Using power analysis, we estimated that with 14 subjects in each group we could detect effects of $d = 1.0$ with sufficient power ($1 - \beta > .80$; given $\alpha = 0.05$, one-sided). Recruitment was stopped after the intended 30 subjects had participated in the experiment.

A researcher in Switzerland who was not directly involved in conducting the experiment and who had no contact to the participants, generated the randomized allocation sequence. MATLAB was used for the randomization, whose underlying random number generator uses the Mersenne Twister algorithm by default[28]. This researcher ensured that the allocation sequence was concealed from those who recruited and assigned the participants. Participants were assigned to a condition according to the allocation sequence in the order in which they were included in the study and only after a final decision about inclusion was made, to support concealment. Researchers at Korea University did the enrollment and then assigned participants to the conditions.

Sampling procedure

We recruited participants via ads on the university's website and a bulletin board on campus. Using the following inclusion and exclusion criteria, we checked all interested students and decided about their eligibility for the study. Inclusion criteria were being i) male, ii) between 18 and 65 years of age, iii) right-handed, iv) familiar with using a smartphone, to take part in the ambulatory training, v) having sufficient English language skills to follow the written instructions in the experiment, vi) no indication of color-blindness, vii) no history of cardiovascular or neurological diseases, and viii) no history of a severe mental disorder. After finishing the whole study procedure, we paid each participant 60,000 KRW to compensate for time and effort related to study participation.

The institutional board of Korea University approved the study and all participants gave written informed consent (approval number: KU-IRB-10-38-A-2(E-A-1)(E-A-1)(E-A-3)).

Materials

We used established tools to assess mood and arousal, applied a well-known cognitive task as a stressor in the fMRI experiment, and instructed our participants in four mental strategies, aimed at reducing their stress response during the experiment.

To assess mood, we used the English version of the established multidimensional mood state questionnaire (MDMQ) (original in German "Mehrdimensionaler Befindlichkeitsfragebogen (MDBF)"), which has good psychometric properties[29,30]. The questionnaire measures current mood on three dimensions: good to bad, awake to tired, and calm to nervous. Individual values on each dimension range from 4 to 24 and higher values represent more positive affect, feeling more awake, and calmer, respectively.

We assessed subjective arousal with a non-verbal pictorial rating scale to assess valence, arousal, and dominance, on a 9-point Likert Scale, called Self-Assessment Manikin (SAM)[31]. The arousal rating was labeled with "At the moment, I'm feeling..." and went from "very calm" to "very aroused" in addition to the original pictures. The SAM is an established tool which is used extensively in research. We were only interested in the arousal dimension, because it is clearly linked to a psychological stress response and, thus, have not analyzed the other dimensions of the SAM.

During the rtfMRInf experiment, we induced acute stress using a cognitive task which had previously been used for this purpose and shown to elicit a cardiovascular and neural stress response: the Stroop color-word interference task[32], adapted for the use in fMRI experiments and to be more challenging due to implemented adaptive time constraints[33,34]. We instructed the participants in four mental strategies: Body attention, contemplative repetition (mantra), emotional imagery, and facial expression (make different emotional faces). More details about these strategies and the exact instructions (text and video clips) were published elsewhere[23].

Overall study procedure

We laid out the whole study as a randomised parallel-group study with rtfMRI neurofeedback as the experimental condition and sham-feedback as the control condition. Participants were

blinded about their allocation, while experimenters and those analyzing the data were not. We registered the study before starting recruitment (ClinicalTrials.gov, identifier NCT01921088). Over the course of the study, participants visited the laboratory three times and conducted 13 days of smartphone-based ambulatory mental training between the two main experimental visits. We conducted the study at the Korea University, Seoul, Republic of Korea (RRID:SCR_004095) between August and October of 2013.

Initially, we screened all interested students in a short telephone interview to check for their history of diseases and mental disorders described in the exclusion criteria above. On a first visit to the laboratory, we then further checked their eligibility based on all additional inclusion and exclusion criteria with a set of questionnaires. There, we also instructed participants about the whole study and the four mental strategies.

After deciding upon the final inclusion in the study, participants then visited the laboratory two more times for the main rtfMRInf experiments. These two visits were 14 days apart and during the 13 days in-between, participants took part in a smartphone-based ambulatory mental training, where they applied the mental strategies they had already used during the experiment in short daily sessions. They were guided through the training with video clips and questionnaires on their smartphones.

We here report data from the first laboratory visit (screening day) and the first experiment day and will, thus, refer to the latter day simply as "experiment day". More details on the procedures, especially regarding the ambulatory training, have been reported elsewhere[23].

Experimental procedure

With regard to the first experiment day, the experimental procedure contained the following phases: Structural scans (1 min), where the previously defined broad regions of interest for the neurofeedback training were localized; *Functional localizer* phase (13 min), where participants did the Stroop task and the individual regions of interest could be pinpointed, to ensure participants get a feedback signal from areas active during the task; resting phase (6 min); *Neurofeedback-only* (i.e., without Stroop) phase (9 min), where participants first had to apply the four learned mental strategies in turn, and then continue using the strategy which worked best for them, and also do neurofeedback; resting phase (6 min); phase with additional structural scans (8 min); *Neurofeedback with Stroop* (13 min), where subjects used both, the mental strategies and the neurofeedback signal to actively modulate their brain activity associated with the stressor; resting phase (6 min); Stroop-only phase (13 min), where subjects only used the mental strategies to reduce their stress response; resting phase (2 min).

The Stroop task runs were made up of 8 blocks each; congruent and incongruent trials were alternated. During the neurofeedback phases, we presented the feedback signal continuously on one side of the screen and (if applicable) the Stroop task on the other side. We assessed current mood (MDMQ questionnaire) once before and once after the whole fMRI experiment and arousal (with the SAMs) after each individual phase of the experiment.

Neurofeedback

We defined a set of regions of interest (ROIs) encompassing the left and right anterior cingulate cortex (ACC) and insular cortex (IC), based on previously found brain activity associated with the Stroop task[33,35]. The anatomical ROI was defined from the automated anatomical labeling (AAL) map and Brodmann's area (BA) map atlases available in MRIcron (https://www.nitrc.org/projects/mricron). The intersection of the AAL 29/30 and the BA 48 were defined as the anatomical ROI for the IC and the intersection of the AAL 31/32 and BA 24/32/33 was defined as the anatomical ROI for the ACC. The use of the both the AAL and BA atlas was because the intersected areas from the two atlases has provided a functionally distinct area compared to the area defined from either one of the two atlas[36].

Within this set of ROIs, a more precise individual ROI was localized during the functional localizer phase for each participant. The recorded and processed brain activity of the individual ROIs was fed back to the participants in near real-time. Participants saw the feedback signal abstracted as a white, moving thermometer-like bar on a black background, which went up and down depending on the signal strength, indicating the divergence from the baseline activity level. We instructed them to reduce the activity of the ROIs using this information, by applying the mental strategies they had learned and the information from the feedback signal. Sham-feedback for the control condition was the recording of the feedback signal from another participant.

We acquired the MRI data with a 3T Siemens Tim Trio scanner with a 12-channel head coil (Erlangen, Germany). To measure the BOLD signal, we applied a standard gradient-echo EPI pulse sequence[37] using the following specifications for rtfMRInf: repetition time (TR) = 1500 ms, echo time = 25 ms, field of view 240*240 mm, matrix size 64*64, voxel size = 3.75*3.75*5 mm, flip angle 90, and 30 interleaved slices with 5mm thickness at approximately 30 oblique to the AC-PC line without a gap[38,39].

We calculated individual ROIs for each participant during the functional localizer phase as follows: EPI preprocessing (head motion correction for six parameters, spatial smoothing with an 8 mm full-width at half maximum Gaussian kernel); estimation of beta-value maps for each incongruent and congruent Stroop trial via general linear model (GLM) implemented in SPM to get a contrast map for "incongruent > congruent Stroop trials"; calculating the neurofeedback signal then from the intersection map between ROIs from the GLM and the predefined set of ROIs. Once a t-contrast map was obtained from the functional localizer run, a default statistical threshold of $p < 0.01$ was used to select the significantly active voxels from the incongruent compared to the congruent condition and consequently, these voxels entailed the functional ROI. The intersection of the functional ROI and anatomical ROI was used as the ROI for the rtfMRI-NF runs. Before the rtfMRI-NF run, the default statistical threshold (i.e., $p < 0.01$) was adjusted to make sure

reasonable number of voxels were included in the ROI for the NF runs. The average number of voxels (+/- standard deviation) in the ROIs were 250.7 +/- 83.9 for the experimental group and 289.2 +/- 80.5 for the control group. The number of voxels between groups were not statistically different (t-score = -1.27 from two-sample t-test; uncorrected p = 0.22; 95% CI = [-100.7, 23.8]).

To calculate the neurofeedback signal, we first removed possible artifacts from the raw BOLD signal of the individual ROIs, applying a bandpass-filter (0.008 - 0.1 Hz) using a third-order elliptic digital filter to avoid low-frequency linear drift[37]. Next, we linearly detrended the median BOLD signals within each of the ROIs as well as the whole-brain area. We then averaged the values between the 10th and 30th percentile during the cross-fixation period, using this as the baseline BOLD intensity (for ROI and whole-brain area). Percentage signal change (PSC) of the ROI relative to the whole-brain area were then estimated voxel-wise, by subtracting the estimated whole-brain PSC from the ROI PSC. This PSC difference was used as the neurofeedback signal. Finally, we averaged the signal over the last three TR periods in order to reduce potential high-frequency fluctuations occurring due to cardiac-and respiratory-related activity.

Data analysis

All offline data analysis was conducted using the software package R (version 3.5.1 and later; RRID:SCR_001905)[40] and specific further packages for R as follows: "lme4" (RRID:SCR_015654) and "lmerTest" (RRID:SCR_015656)[41], to conduct the mixed effects models, "dplyr" (RRID:SCR_016708) and "tidyr" (RRID:SCR_017102)[42] for data preparation, and "ggplot2" (RRID:SCR_014601)[43] and "ggpubr"[44] to create and export data visualizations. For online fMRI data preparation, analysis, feedback signal calculation, and neurofeedback presentation as described above, we used MATLAB (The MathWorks, Inc., Natick, MA, USA; RRID:SCR_001622) with SPM8 (RRID:SCR_007037).

To take into account the longitudinal nature of the mood data (two measurements, before and after the fMRI session), we used linear mixed effects models. Our models included the following factors: fixed effects Time (prescan, postscan), Condition (experimental, control), and the interaction Time*Condition, and random intercept for each participant. We estimated three models, one for each of the mood dimensions as dependent variable. Together with beta values, we report 95% confidence intervals of two-sided tests using an alpha-level of 0.05 to determine statistical significance.

Results

Participant flow

The flow of participants, from enrollment to allocation and analysis, is given in Figure 1 in a flow diagram consistent with the Consolidated Standards of Reporting Trials (CONSORT).

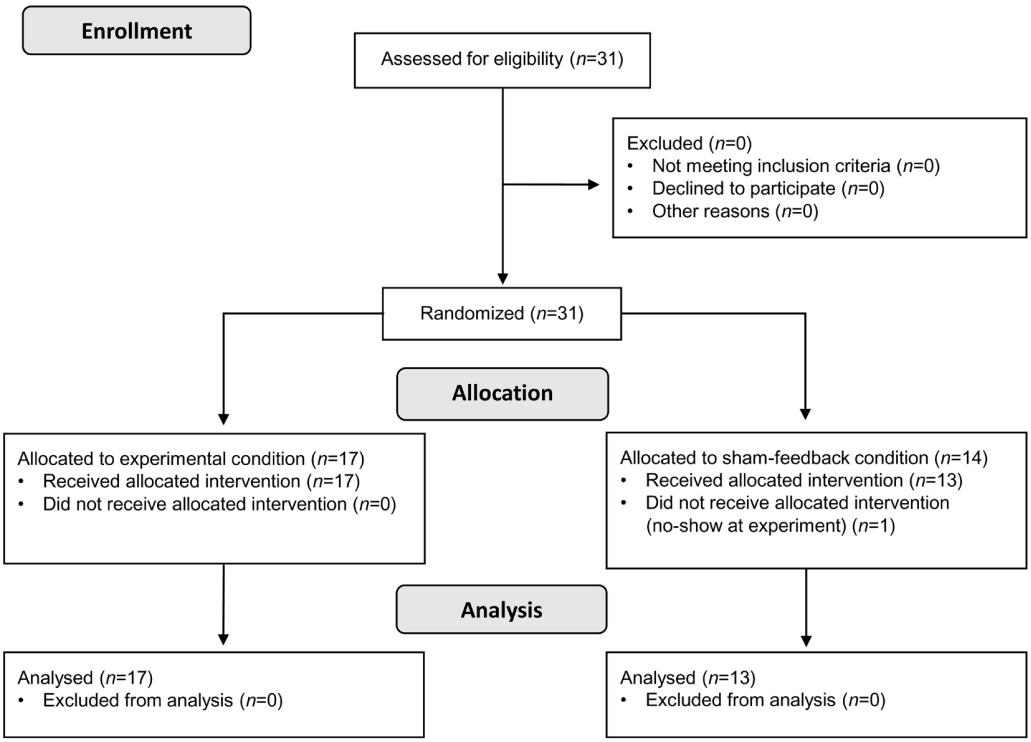

Figure 1. CONSORT flow diagram.

Mood

Mood scores were assessed with the MDMQ once before and once after the fMRI session. Results of individual mixed models for the three mood dimensions are presented in Table 1, and descriptive statistics can be found in the interaction plots in Figure 2. In the mood dimensions good/bad and awake/tired, we saw lower values after the fMRI session than before in both conditions, leading to a significant main effect of time. In the calm/nervous dimension, a slight drop in values was present only in the experimental condition, but neither the time effect nor the interaction with condition was significant in this model. None of these models, to determine effects on mood, showed a significant main effect for condition or an interaction between time and condition.

Table 1. Mixed models results of mood data.

Mood good/bad				
Fixed Effects				
		95%CI		
Predictors	***Estimates***	***lower***	***upper***	***p***
(Intercept)	15.7	14.63	16.76	<0.001
Time (after fMRI-session)	-0.77	-1.31	-0.23	0.009
Condition (control)	0.4	-0.67	1.47	0.467
Time*Condition	0.17	-0.37	0.71	0.535
Random Effects				
Marginal R^2 / Conditional R^2	σ^2	τ_{00} ***subject***	***ICC subject***	***Observations***
0.072 / 0.632	4.28	6.5	0.6	59
Mood awake/tired				
Fixed Effects				
		95%CI		
Predictors	***Estimates***	***lower***	***upper***	***p***
(Intercept)	14.769	13.681	15.857	<0.001
Time (after fMRI-session)	-0.652	-1.116	-0.187	0.01
Condition (control)	0.769	-0.319	1.857	0.177
Time*Condition	0.113	-0.351	0.577	0.637
Random Effects				
Marginal R^2 / Conditional R^2	σ^2	τ_{00} ***subject***	***ICC subject***	***Observations***
0.090 / 0.720	3.31	7.43	0.69	60
Mood calm/nervous				
Fixed Effects				
		95%CI		
Predictors	***Estimates***	***lower***	***upper***	***p***
(Intercept)	15.35	14.32	16.38	<0.001
Time (after fMRI-session)	-0.28	-0.83	0.27	0.331
Condition (control)	0.5	-0.53	1.53	0.352
Time*Condition	0.28	-0.27	0.83	0.331
Random Effects				
Marginal R^2 / Conditional R^2	σ^2	τ_{00} ***subject***	***ICC subject***	***Observations***
0.039 / 0.573	4.62	5.78	0.56	59

Note. σ^2 = within-group variance, τ_{00} = between-group variance, ICC = intraclass correlation coefficient, CI = confidence interval. Factor predictors were coded using effect/deviant coding to increase interpretability of the fixed effects. Comparison from the mean intercept of the factor to the level names in parentheses for each factor. In the good/bad and calm/nervous models, there was one missing value each.

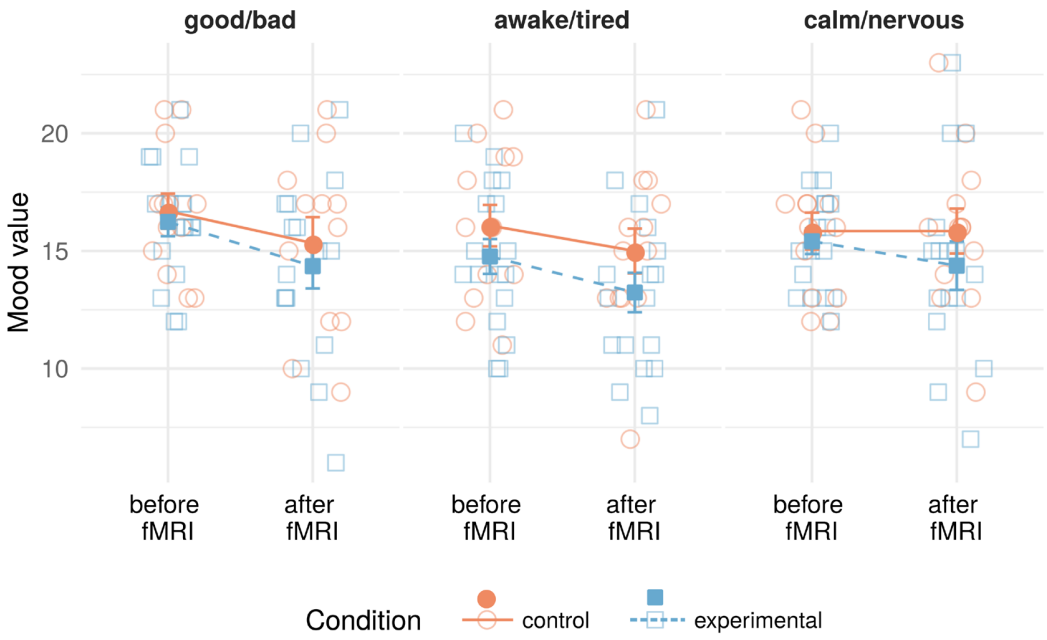

Figure 2. Mood values reported before and after fMRI session for experimental and control condition. Lighter empty symbols in the background are individual data points (jittered on the x-axis to avoid overplotting), while filled symbols with error bars are condition group values (means and standard errors).

Arousal

We calculated Welch two sample t-tests for unequal variances to assess differences in SAM arousal values between the experimental and control conditions. To account for heteroscedasticity, these tests model different variances for both levels of the factor condition. Descriptive values for subjective arousal can be found in Figure 3. In the "Neurofeedback-only" phase, we found SAM arousal to be significantly higher for participants in the experimental condition [t(26.6)=-2.216, 95%CI[-2.188, -0.083], p=0.035, (two-tailed test)], as compared to those in the control condition. In the phase "Neurofeedback with Stroop", SAM arousal was also significantly higher in the experimental condition [t(27.9)=-3.252, 95%CI[-2.685, -0.609], p=0.003, (two-tailed test)]. This difference was not present in the "Functional localizer" phase, before the neurofeedback intervention started [t(24.1)=-1.429, 95%CI[-1.869, 0.339], p=0.166, (two-tailed test)].

Discussion

Subjective arousal was higher after neurofeedback training as compared to the sham-feedback control. This was true when the stressor task was present and when not. In our mood data, we could not observe changes specifically related to real neurofeedback, but participants in both conditions reported worse mood and being more tired after the fMRI session as compared to before.

These findings pose several questions: First, why did subjective arousal rise, contrary to our goal to reduce stress with our intervention? Arousal rose for experimental condition participants but not for those in the control condition, even when neurofeedback was practiced without a stressor. This finding is in contrast to the assumption that with neurofeedback, subjects reduce their stress response going along with reduced subjective arousal. The finding is, however, in line with the assumption that the cognitive demand on subjects in the experimental condition was higher as compared to subjects in the control condition. Let us recapitulate what participants did in this phase of the experiment: They applied previously learned mental strategies and used the feedback signal from their ACC and IC, trying to reduce the activity in these brain regions. This was the same for experimental and control condition participants. The only difference was the kind of feedback signal they saw (real or sham).

One possible explanation supporting the idea of increased cognitive demand in the experimental condition is the multitasking situation, present in the experiment. Participants had to do several tasks simultaneously. This might have lead to increased mental load in subjects who got real feedback compared to those who got sham-feedback, because those receiving sham-feedback might have (consciously or unconsciously) realized that the shown signal was not contingent with their brain activity. They might then have given less attention to this signal and the neurofeedback training and could focus better on other task(s) (applying mental strategies and solving the Stroop task). Arousal levels might, thus, here be an indicator for multitasking and increased mental load instead of an effect of the Stroop-induced stress. In this sense, the multitasking aspect of the experiment may have itself become a stressor, because it increased the cognitive demand of the participant.

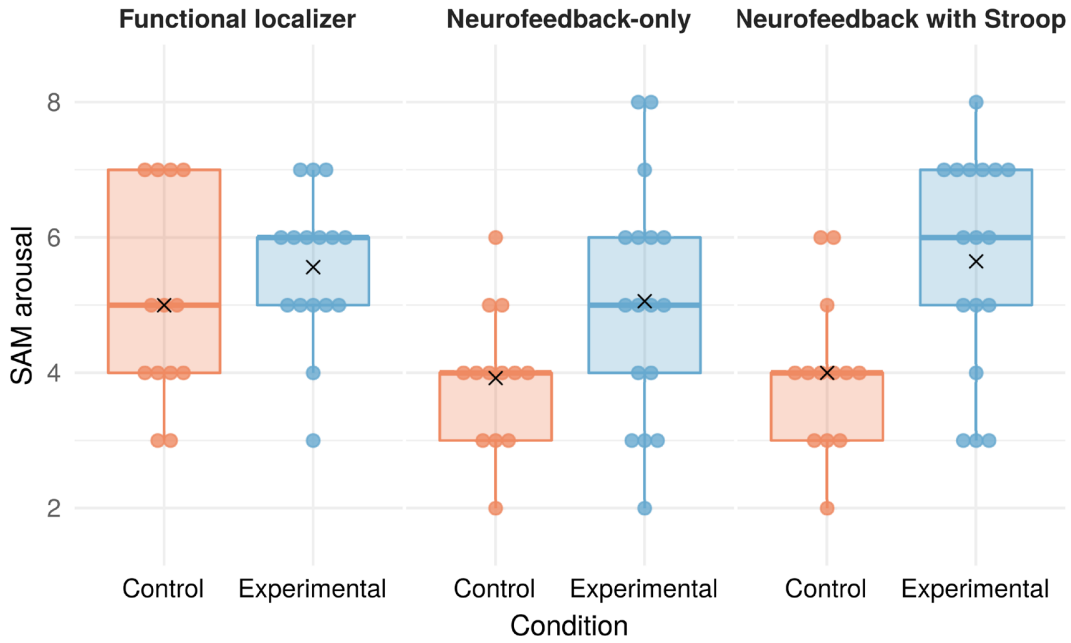

Figure 3. Subjective arousal by condition and experiment phase. Combination of dot plot with individual data points and a boxplot for each condition group. The boxplot's lower and upper hinges mark the 25th and 75th percentiles. Whiskers extend from the hinges to the largest/smallest value up to 1.5 * the inter-quartile range. Black X shapes mark the condition group means. There was one missing value in the experimental condition during the functional localizer phase.

The second set of questions concerning our results is: Why could we not observe any statistically significant mood changes related to the intervention and what could explain the increased tiredness and worse mood after the fMRI session?

We observed no statistically significant mood changes associated with neurofeedback, even though we would have expected better mood after the training in accordance with the study aim to reduce the physiological and psychological stress response with the help of neurofeedback. This could be linked to one limitation in the experimental design, namely that we measured mood only completely before and after the fMRI session. The observed mood effects can, thus, primarily be interpreted in relation to the participant's experience over the whole session and unfortunately they can not be matched to putative mood changes related to single experiment phases. Interestingly, subjective arousal, which was measured directly after each experiment phase during the fMRI session, did show differences between the conditions. We can, thus, assume that the sampling rate of mood might not have been fine-grained enough to pick up differences between the conditions and was only able to represent the overall experiment effects on all participants.

Regarding tiredness, fatigue due to the experiment and cognitive demand is expected. A one hour fMRI session is tiring and such overall effects might overshadow the miniscule differences between conditions due to the manipulation (real vs. sham feedback). Especially also since the neurofeedback manipulation was only present in some phases of the experiment. The lower awake/tired mood values after the experiment are, thus, not surprising. Participants may become tired after a demanding experiment in an fMRI scanner where they have to repeatedly solve a monotonous cognitive task. Furthermore, we expected our participants to relax and calm down. Thus, their indication of being more tired can be interpreted in line with what they actually did.

To explain the decrease in the good/bad mood dimension, we can look at the individual items in the questionnaire that made up this dimension: Subjects rated to what degree they felt uncomfortable, content, discontent, good, bad, happy, unhappy, great, superb, and wonderful. For example, it is unlikely to feel more comfortable and content after the experiment, given that lying in an fMRI scanner can be somewhat uncomfortable, and considering that participants were challenged with a cognitive task with adaptive difficulty, ensuring that they did not perform too well. Even if participants could modulate their immediate stress response, the overall mood change from before to after the experiment towards a worse mood might, thus, be explainable.

We also did not target to specifically change mood with our intervention. In comparison to another rtfMRI study, which did exactly that[21], we used different target brain regions. Where these researchers targeted brain regions that most highly reflected activity differences in response to positive vs. neutral images, we focused on regions associated with our stressor task. Our modulated regions were thus less likely to be directly

involved in supporting positive mood and we could only expect a potential side-effect in the mood due to the down-regulation of the stress response.

Future studies should aim to overcome the above-mentioned limitations, including limited time resolution in mood assessment: They could profit from using a shorter mood assessment instrument that can be applied in higher frequency. One example is a visual analog scale (VAS) to rate perceived stress, which could be implemented during an fMRI experiment and which allows to sample rapidly and repeatedly, yet with lower precision as compared to the MDMQ. Longer questionnaires like the applied MDMQ interrupt the experiment for a longer time and are thus not ideal to be applied in higher frequency. Another potential limitation is that we used questionnaires in English but not in the Korean mother tongue of our participants. However, we ensured that all participants had sufficient English language skills and the content of the questionnaires consisted of rather simple English language, so that language issues can largely be ruled out.

Broader implications for future research include a notion that the multitasking situation during an experiment can itself influence the measured values. While it is important to make the best of experimental time for economic reasons and to avoid prolonging an experiment unnecessarily, overloading an experiment might result in unexpected and intertwined effects. In our case, the multitasking present during the experiment might have led to our finding of increased arousal connected to the neurofeedback intervention. Even though challenging, future rtfMRInf studies on stress should try to prevent multitasking situations as good as possible. One could also more explicitly look at this multitasking aspect and conduct experiments to elucidate this component in the context of rtfMRInf research. Further, it would be interesting to explore, whether subjective and brain reactivity to stress is associated across subjects; investigating the relationship between self-reported psychological factors and the brain activity changes during neurofeedback. Analyses of data from the second experiment day, conducted two weeks later, may also add information on potential delayed effects of rtfMRInf training.

We had set out asking whether rtfMRInf to modulate the stress response would influence participants' subjective perception of mood and arousal. The mood effects reflected the overall experimental experience due to sampling only before and after the fMRI session, and probably reflected rather general fatigue due to the cognitively demanding experiment than specific neurofeedback effects. To the best of our knowledge, we are the first to report a phenomenon of neurofeedback-related arousal: With regard to arousal, our findings are in line with the assumption that the multitasking nature of conducting neurofeedback during a stress task may have increased acute stress perceived by our participants, being in contrast to short-term neurofeedback effects on reduced subjective indicators of stress. Future studies should take into account multitasking situations in the experimental design, and further elucidate the neurofeedback-related arousal phenomenon, especially in the context of stress.

Data availability

Underlying data

Full underlying (non-aggregated) data cannot be made publicly available since the ethics approval of this study does not cover openly publishing non-aggregated data.

In order to access this data, it must be requested from the corresponding author. Data requestors will have to provide: i) written description and legally binding confirmation that their data use is within the scope of the study; ii) detailed written description and legally binding confirmation of their actions to be taken to protect the data (e.g., with regard to transfer, storage, back-up, destruction, misuse, and use by other parties), as legally required and to current national and international standards (data protection concept); and iii) legally binding and written confirmation and description that their use of this data is in line with all applicable national and international laws (e.g., the General Data Protection Regulation of the EU).

Reporting guidelines

Open Science Framework: CONSORT checklist for "Does fMRI neurofeedback in the context of stress influence mood and arousal? A randomised controlled trial with parallel group design". https://doi.org/10.17605/OSF.IO/XFQHZ[45].

Acknowledgements

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Reviewer Report 26 July 2019

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✔ **Ryuichiro Hashimoto**
[1] Medical Institute of Developmental Disabilities Research, Showa University, Tokyo, Japan
[2] Tokyo Metropolitan University, Hachioji, Japan

This is a well-done study of fMRI-neurofeedback, which is gaining considerable attention as a potential new method for clinical intervention and increasing mental functions. The study is commended for its rigorous sampling and other procedures for the randomized controlled trial. The reviewer is particularly impressed by rigid applications of statistical tests and all the information necessary for assessing the effect of neurofeedback was clearly presented, including effect size and 95%CI. Overall, the study provides significant information for researchers who are interested in the application of fMRI-neurofeedback for various purposes.

The reviewer would like to raise some concerns in the hope of improving the clarity of the study even more as follows:
Although other parts of the study designs are well written, I feel that the procedures of neurofeedback are less satisfactory. Particularly, the reviewer would like to ask the following points:

1. The authors seemed to have identified ROI in the individual brain using a contrast map of incongruent > congruent. How was the statistical threshold determined? How different were identified ROIs between individuals? Probably mean and SD of the cluster sizes should be described. How were ACC and IC combined?

2. Subjects were instructed to apply one of the 4 mental strategies that were given to them before the study. What were they actually? The author stated that each subject selected the best one that worked for him/herself (page 5 left column), how was the "best" one determined? The reviewer would like to know whether and how the 4 mental strategies are expected to change ACC and IC activation.

3. The reviewer could not locate the description of the length of each fMRI run, including functional localizer, NF only, resting-state, NF+Stroop, and Stroop-only.

4. In page 5, it says that "We instructed them to *modulate* the activity of the ROIs ..." . Does "modulate" include both increase and decrease activation, or only decrease activation? In page 9

(left column), it says "trying to *reduce* the activity in these brain regions".

5. Sham condition. In page 5, it says "sham feedback for the control condition was the recording of the feedback signal from another participant". How was "another participant" selected? Was it selected from the control group or from experiment group or both?

6. Were subjects in the experiment group able to increase scores significantly at the end of the day 1.

7. Was there any relationship between changes in NF scores and psychological scores between individuals?

8. Probably related to (5) and (6), were the degrees of score changes controlled between the experiment and control groups? Can the authors exclude the possibility that the psychological scores related to stress responses are associated with the NF scores?

Minor points

1. The reviewer understands that the participants were Korean university students. On the other hand, the authors used the English version of the MDMQ. Application of the psychological test in a foreign language might affect the subjects' responses depending on the proficiency of English.

2. The reviewer feels that the study will become more significant analyzing the data of the second fMRI experiment after the mental training rather than focusing on the first fMRI experiment. Do we expect the report of the second fMRI experiment come up in the future?

Is the work clearly and accurately presented and does it cite the current literature?
Yes

Is the study design appropriate and is the work technically sound?
Yes

Are sufficient details of methods and analysis provided to allow replication by others?
Partly

If applicable, is the statistical analysis and its interpretation appropriate?
Yes

Are all the source data underlying the results available to ensure full reproducibility?
Partly

Are the conclusions drawn adequately supported by the results?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: neuroimaging

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Author Response 22 Nov 2019

Angelo Belardi, University of Basel, Basel, Switzerland

Point by point responses to the comments by Reviewer R. Hashimoto
Replies are preceded by "***"

General comment:
This is a well-done study of fMRI-neurofeedback, which is gaining considerable attention as a potential new method for clinical intervention and increasing mental functions. The study is commended for its rigorous sampling and other procedures for the randomized controlled trial. The reviewer is particularly impressed by rigid applications of statistical tests and all the information necessary for assessing the effect of neurofeedback was clearly presented, including effect size and 95%CI. Overall, the study provides significant information for researchers who are interested in the application of fMRI-neurofeedback for various purposes.

*** We thank the reviewer for the thoughtful and supportive feedback on our publication. Below, we individually address all major and minor points.

****

Major points:

The reviewer would like to raise some concerns in the hope of improving the clarity of the study even
more as follows:
Although other parts of the study designs are well written, I feel that the procedures of neurofeedback are less satisfactory.

***1:** The authors seemed to have identified ROI in the individual brain using a contrast map of incongruent > congruent. How was the statistical threshold determined? How different were identified ROIs between individuals? Probably mean and SD of the cluster sizes should be described. How were ACC and IC combined?*

*** We thank the reviewer for this insightful feedback that we used to add relevant parts to the methods section on the description of the neurofeedback procedures: Once a t-contrast map (i.e., incongruent > congruent) was obtained from the functional localizer run, a default statistical threshold of $p < 0.01$ was used to select the significantly active voxels from the incongruent compared to the congruent condition and consequently, these voxels entailed the functional region-of-interest (ROI).

The intersection of the functional ROI and anatomical ROI was used as the ROI for the rtfMRI-NF runs. Before the rtfMRI-NF run, the default statistical threshold (i.e., $p < 0.01$) was adjusted to make sure reasonable number of voxels were included in the ROI for the NF runs.

The average number of voxels (+/- standard deviation) in the ROIs were 250.7 +/- 83.9 for the experimental group and 289.2 +/- 80.5 for the control group. The number of voxels between groups were not statistically different (t-score = -1.27 from two-sample t-test; uncorrected $p = 0.22$; 95% confidence interval = [-100.7, 23.8]).

Regarding the combination of the pre-determined ROIs, an anatomical ROI to include the ACC and

IC was defined from the automated anatomical labeling (AAL) map and Brodmann's area (BA) map atlases available in MRIcron (https://www.nitrc.org/projects/mricron). The intersection of the AAL 29/30 and the BA 48 were defined as the anatomical ROI for the IC and the intersection of the AAL 31/32 and BA 24/32/33 was defined as the anatomical ROI for the ACC. The use of the both the AAL and BA atlas was because the intersected areas from the two atlases has provided a functionally distinct area compared to the area defined from either one of the two atlas [1]. We added this information in the revised version of the manuscript.

2: *Subjects were instructed to apply one of the 4 mental strategies that were given to them before the study. What were they actually? The author stated that each subject selected the best one that worked for him/herself (page 5 left column), how was the "best" one determined? The reviewer would like to know whether and how the 4 mental strategies are expected to change ACC and IC activation.*

*** We thank the reviewer for this comment, allowing us to clarifying on this relevant aspect of the methods: The four mental strategies are described in detail in an earlier publication (open access) by the authors, from which the written instructions for each strategy are available in detail [2]. We now highlight more clearly where this information on the instructions can be found. The participants were free to choose one of the strategies. There was no instruction on how they had to determine which strategy worked “best” for them. It was a subjective choice based on the experience the subjects made while trying out all four strategies in the scanner, during the “neurofeedback without Stroop” phase, as we assumed that subjective evaluation of the strategies would a) best indicate which strategy indeed worked best for the individual subject and b) lead to the best adherence of the subject using this strategy later on.
Based on previous studies on the strategies’ potential in relation to stress reduction, we expected that they could reduce these ROIs activity related to the stress response, since both ROIs had been found to be involved in the stress response elicited by the Stroop task [3, 4].

3: *The reviewer could not locate the description of the length of each fMRI run, including functional localizer, NF only, resting-state, NF+Stroop, and Stroop-only.*

*** As suggested by the reviewer, we added the duration of each phase of the fMRI experiment to the “Methods / Experimental procedure” section in the revised manuscript.

4: *In page 5, it says that "We instructed them to modulate the activity of the ROIs ..." . Does "modulate" include both increase and decrease activation, or only decrease activation? In page 9 (left column), it says "trying to reduce the activity in these brain regions".*

*** Indeed, the instruction was to decrease the activity. We adjusted the first cited sentence to specify this.

5: *Sham condition. In page 5, it says "sham feedback for the control condition was the recording of the feedback signal from another participant". How was "another participant" selected? Was it selected from the control group or from experiment group or both?*

*** Sham feedback was always the recording from a participant of the experimental group. Each activity recording used for sham feedback was taken from the preceding participant of the experimental group.

6: *Were subjects in the experiment group able to increase scores significantly at the end of the day 1.*

*** If we understand correctly, the reviewer here refers to the modulation of brain activity. These data are not reported in the current publication and will instead be included in another publication reporting the results from the main outcomes of the experiment (fMRI and blood pressure data).

7: *Was there any relationship between changes in NF scores and psychological scores between individuals?*

*** See reply to point 6 above; We thank the reviewer for pointing this out and added a respective sentence in the discussion section, highlighting that this would be an interesting additional question to be addressed.

8: *Probably related to (5) and (6), were the degrees of score changes controlled between the experiment and control groups? Can the authors exclude the possibility that the psychological scores related to stress responses are associated with the NF scores?*

*** We did not control or adjust for the degree of changes in psychological scores between conditions, but took into account the factor condition, by modeling it in our analyses. With regard to any relations with brain responses, see replies to questions 6 and 7.

Minor points:

1: The reviewer understands that the participants were Korean university students. On the other hand, the authors used the English version of the MDMQ. Application of the psychological test in a foreign language might affect the subjects' responses depending on the proficiency of English.

*** We agree that this might generally be an issue. To minimize this problem, we ensured that only students with sufficient English language skills were included in the study. We added a respective sentence in the discussion section of the manuscript, pointing out this limitation of the study.

2: The reviewer feels that the study will become more significant analyzing the data of the second fMRI experiment after the mental training rather than focusing on the first fMRI experiment. Do we expect the report of the second fMRI experiment come up in the future?

*** We agree with the reviewer that the data from the second part of the fMRI experiments would add valuable information; yet habituation of the stress reactivity, the size of the stress-reactivity is getting smaller over time, makes it increasingly difficult to interpret the signals. To focus on the initial question and to keep the publication readable, we hence chose to focus on the first experiment to see the effects on the first responses to the Stroop task and the mental strategies. Further, given that we didn't see significant short-term differences between the conditions regarding mood, we do not expect them to develop later, even though we agree that this may theoretically happen and be an interesting topic for further study. We added a respective paragraph in the discussion section.

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Competing Interests: No competing interests were disclosed.

2.3 Publication 3: Mediation analysis of triple networks revealed functional feature of mindfulness from real-time fMRI neurofeedback

Full reference: H.-C. Kim, M. Tegethoff, G. Meinlschmidt, E. Stalujanis, A. Belardi, S. Jo, J. Lee, D.-Y. Kim, S.-S. Yoo, and J.-H. Lee. Mediation analysis of triple networks revealed functional feature of mindfulness from real-time fMRI neurofeedback. *NeuroImage*, 195:409–432, jul 2019. ISSN 1053-8119. doi:10.1016/j.neuroimage.2019.03.066

Mediation analysis of triple networks revealed functional feature of mindfulness from real-time fMRI neurofeedback

Hyun-Chul Kim[1], Marion Tegethoff[2], Gunther Meinlschmidt[3,4,5], Esther Stalujanis[2,5], Angelo Belardi[2], Sungman Jo[1], Juhyeon Lee[1], Dong-Youl Kim[1], Seung-Schik Yoo[6], Jong-Hwan Lee[1]

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Word count: 12,180 words (excluding a title page, abstract, appendix, references, 12 figures and legends, three tables, and supplementary materials)

Short title: Mediation analysis of triple networks from rtfMRI-NF based mindfulness training

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Abstract

The triple networks, namely the default-mode network (DMN), the central executive network (CEN), and the salience network (SN), play crucial roles in disorders of the brain, as well as in basic neuroscientific processes such as mindfulness. However, currently, there is no consensus on the underlying functional features of the triple networks associated with mindfulness. In this study, we tested the hypothesis that: (a) the partial regression coefficient (i.e., slope) from the SN to the DMN, mediated by the CEN, would be one of the potential mindfulness features in the real-time functional magnetic resonance imaging (rtfMRI) neurofeedback (NF) setting, and (b) this slope level may be enhanced by rtfMRI-NF training. Sixty healthy mindfulness-naïve males participated in an MRI session consisting of two non-rtfMRI-runs, followed by two rtfMRI-NF runs and one transfer run. Once the regions-of-interest of each of the triple networks were defined using the non-rtfMRI-runs, the slope level was calculated by mediation analysis and used as neurofeedback information, in the form of a thermometer bar, to assist with participant mindfulness during the rtfMRI-NF runs. The participants were asked to increase the level of the thermometer bar while deploying a mindfulness strategy, which consisted of focusing attention on the physical sensations of breathing. rtfMRI-NF training was conducted as part of a randomized controlled trial design, in which participants were randomly assigned to either an experimental group or a control group. The participants in the experimental group received contingent neurofeedback information, which was obtained from their own brain signals, whereas the participants in the control group received non-contingent neurofeedback information that originated from matched participants in the experimental group. Our results indicated that the slope level from the SN to the DMN, mediated by the CEN, was associated with mindfulness score (rtfMRI-NF runs: r = 0.53, p = 0.007; p-value was corrected from 10,000 random permutations) and with task-performance feedback score (rtfMRI-NF run: r = 0.61, p = 0.001) in the experimental group only. In addition, during the rtfMRI-NF runs the level of the partial regression coefficient feature was substantially increased in the experimental group compared to the control group ($p < 0.05$ from the paired t-test; the p-value was corrected from 10,000 random permutations). To the best of our knowledge, this is the first study to demonstrate a partial regression coefficient feature of mindfulness in the rtfMRI-NF setting obtained by triple network mediation analysis, as well as the possibility of enhancement of the partial regression coefficient feature by rtfMRI-NF training.

Keywords: Central executive network, contemplative science, default-mode network, functional connectivity, functional magnetic resonance imaging, mediation analysis, mindfulness, real-time fMRI neurofeedback, salience network

Introduction

Three prominent, functionally-connected large-scale networks, comprised of the default-mode network (DMN), the central executive network (CEN), and the salience network (SN), are collectively known as the triple network (Menon, 2011). These triple networks reflect typical developmental changes, including those of emotional dysfunction, aberrant saliency mapping, and cognitive dysfunction, which are characteristics of a range of mental and neurological disorders such as anxiety disorders, depressive disorders, autism, schizophrenia, Alzheimer's disease, and frontotemporal dementia (Menon, 2011; Touroutoglou et al., 2015; Uddin et al., 2011; Young et al., 2017). The DMN includes the posterior cingulate cortex (PCC) and the ventromedial prefrontal cortex (vmPFC) and is known for its role in self-related (i.e., internally directed) perception (Brewer and Garrison, 2014; Brewer et al., 2011; Fair et al., 2008; Mooneyham et al., 2016; Sheline et al., 2009; Sridharan et al., 2008; Uddin, 2015). On the other hand, the CEN includes the posterior parietal cortex and the dorsolateral prefrontal cortex (dlPFC) and is known for its function in goal-oriented (i.e., externally directed) cognition (Beaty et al., 2015; Christoff et al., 2016; Mooneyham et al., 2016; Sridharan et al., 2008; Uddin, 2015). In contrast, the SN includes the dorsal anterior insular cortex (dAIC) and the dorsal anterior cingulate cortex (dACC) and is known as the hub of interoceptive perception (Barrett and Simmons, 2015; Mooneyham et al., 2016). In addition, the SN influences signals in the DMN and the CEN causally and dynamically (Mooneyham et al., 2016; Uddin, 2015).

In recent years, mindfulness has gained increasing interest across a variety of research fields because of its potential benefits, including improvements in executive function, emotional regulation, working memory, and vigilance. Furthermore, mindfulness has pre-clinical benefits applicable to a broad range of mental disorders such as addictions, anxiety disorders, and depressive disorders (Baer, 2003; Diamond and Lee, 2011; Dunne, 2017; Hofmann et al., 2010; Miller et al., 1995; Mooneyham et al., 2016; Morgan, 2003; Wang et al., 2018; Weick et al., 2008; Zeidan et al., 2010). Interestingly, a particular set of brain regions involved with mindfulness appears to lie within the triple network (Brewer et al., 2011; Dickenson et al., 2013; Doll et al., 2016; Hasenkamp and Barsalou, 2012; Lutz et

al., 2015; Mooneyham et al., 2016). Accordingly, recent neuroimaging studies on mindfulness have focused on changes in functional connectivity (FC) within and/or between the triple networks (Bilevicius et al., 2018; Brewer et al., 2011; Creswell et al., 2016; Doll et al., 2016; Hasenkamp and Barsalou, 2012; King et al., 2016; Lim et al., 2018; Lutz et al., 2015; Marusak et al., 2018; Mooneyham et al., 2016; Peters et al., 2016; Shaurya Prakash et al., 2012; Taren et al., 2017). Two findings consistently emerge from these previous studies: first, an increase of FC within the DMN (e.g., between the posterior DMN, including the PCC, and the anterior DMN, including the vmPFC), potentially because of an increase in self-referential processing (Hasenkamp and Barsalou, 2012; Mooneyham et al., 2016; Wells et al., 2013), and, second, an increase in FC between the SN and the CEN, potentially because of conscious executive processing (associated with the CEN) of moment-to-moment interoceptive perception (associated with the SN) (Brewer et al., 2011; Hasenkamp and Barsalou, 2012; Mooneyham et al., 2016; Seeley et al., 2007). Other than these findings, likely because of the diversity of mindfulness practices and methodological designs, there has been no unequivocal consensus on the FC features of mindfulness (Doll et al., 2015; Froeliger et al., 2012; Kilpatrick et al., 2011; Lutz et al., 2015; Mooneyham et al., 2016).

Early pioneering work on real-time fMRI-based neurofeedback (rtfMRI-NF) has shown that participants can learn volitional control over their own blood-oxygenation-level-dependent (BOLD) signals (deCharms et al., 2005; Posse et al., 2003; Weiskopf et al., 2004a; Weiskopf et al., 2004b; Weiskopf et al., 2003; Yoo et al., 2004; Yoo and Jolesz, 2002). Since then, a number of studies have demonstrated the utility of rtfMRI-NF successfully. In addition, the applicability of rtfMRI-NF has been extensively discussed in several recent review papers covering a broad range of its basic neuroscientific aspects and pre-clinical applications (Ruiz et al., 2014; Sitaram et al., 2017; Sulzer et al., 2013a; Thibault et al., 2017; Weiskopf, 2012), its use as a tool for clinical interventions (Kim and Birbaumer, 2014; Linden and Turner, 2016; Stoeckel et al., 2014), and advanced techniques such as decoding-based neurofeedback (Watanabe et al., 2017). Furthermore, increasing effort has been made to enhance the level of mindfulness using the rtfMRI-NF method applying the strategy of focusing attention on the physical sensations of breathing. The neurofeedback information (or signal) provided to participants is

calculated by using the BOLD intensities from the PCC that are associated with self-referential processing. Moreover, it has been reported that PCC activation is significantly lower in experienced meditators than non-meditators (Brewer and Garrison, 2014; Garrison et al., 2013). However, a single brain region such as the PCC may be limited in its ability to account for the neuronal underpinnings of complex cognitive processes, including mindfulness under rtfMRI-NF conditions (Garrison et al., 2013; Mooneyham et al., 2016). Instead, information from multiple hubs or the FC of networks of brain regions such as the triple network enables the neuronal underpinnings of mindfulness (Garrison et al., 2013; Mooneyham et al., 2016).

To the best of our knowledge, this is the first study to propose a rtfMRI-NF-based training approach for mindfulness by employing mediation analysis using the triple network to estimate neurofeedback information. To this end, mindfulness-naïve males were recruited to perform rtfMRI-NF-based mindfulness training using the strategy of focusing attention on the physical sensations of breathing (Brewer et al., 2011; Garrison et al., 2013; Meinlschmidt et al., 2016). We expected that (i) this mindfulness strategy would evoke activation in the SN, which is closely linked to visceromotor interoceptive perception (Barrett and Simmons, 2015; Mooneyham et al., 2016; Uddin, 2015) and (ii) the mindfulness status would be reflected in the self-referential processing of the DMN (Brewer and Garrison, 2014; Mooneyham et al., 2016; Uddin, 2015). In addition, the CEN, which is in charge of conscious executive processing, (Mooneyham et al., 2016; Seeley et al., 2007) would also be expected to be involved in rtfMRI-NF-based mindfulness because participants watched neurofeedback information to evaluate their performance with respect to mindfulness.

More specifically, since participants were initiating a mindfulness strategy (i.e., focusing on the sensation of breathing) in a self-paced manner, the strategy was expected to affect the interoceptive perception of the SN. This was expected to be reflected as an inherent mindfulness status via the self-referential processing of the DMN. Thus, the BOLD signal in the SN would be expected to be an independent variable and the BOLD signal in the DMN a dependent variable. The anterior insula has been known to play a causal role in switching between the CEN and DMN, and the CEN and DMN

would undergo competitive interactions to mediate between the external and internal worlds, respectively, depending on task paradigms and stimulus conditions (Bressler and Menon, 2010). The CEN would mediate the processes of interoceptive perception as indicated by the thermometer bar (i.e., between the SN and CEN; external conscious processing) and consequent self-referential processing (i.e., between the CEN and DMN; internal conscious processing). Thus, the BOLD signal in the CEN was adopted as a possible mediator in the mediation analysis. The frontoparietal control system (i.e., CEN in our study) has indeed been reported to be flexible hubs that regulate distributed systems across the sensorimotor and limbic (i.e., interoceptive perception in our study) according to the current task goals being processed by the brain (i.e., mindfulness), in which this control system has been active during mindfulness meditation (Cole et al., 2014). Thus, we hypothesized that: (a) the partial regression coefficient (i.e., slope) from the SN to the DMN, mediated by the CEN, would be one of the potential features of mindfulness in the mediation analysis framework, and (b) this feature of mindfulness would be enhanced by rtfMRI-NF-based mindfulness training. rtfMRI-NF training was conducted as part of a randomized controlled trial design, which included an experimental group (subjects receiving contingent, real, neurofeedback information) and a control group (subjects receiving non-contingent neurofeedback information from matched subjects in the experimental group).

Materials and Methods

Overall study protocol

The data presented in this study were collected within a randomized controlled trial, which was registered at ClinicalTrials.gov (Identifier: NCT03148678; clinicaltrials.gov/ct2/show/NCT03148678). The Institutional Review Board of Korea University approved the entire study protocol, and participants provided written informed consent. All participants were recruited from one site (Korea University) where an MRI session was performed, and another site (University of Basel) managed all the logistics required to perform ambulatory training sessions with the recruited participants. Figure 1a illustrates the overall study procedure along with the time intervals between sessions and the number of included/excluded participants. The detailed information is described in the following subsections.

Telephone interview

Volunteers were recruited from across the university campus using flyers, over the internet, and by word-of-mouth. Interested volunteers were screened for eligibility by telephone interview. Those who met our inclusion criteria (i.e., right handedness, no history of neurological or mental disorders, no previous experience with mindfulness meditation, and being smartphone users) were invited to a face-to-face interview.

Face-to-face interview

First, we reviewed the inclusion criteria for the invited volunteers using the Edinburgh Handedness Inventory (EHI) (Oldfield, 1971) and Patient Health Questionnaire (PHQ) (Spitzer et al., 1999). Also, we collected sociodemographic and self-report information on psychological measures including the Big Five Inventory-10 (BFI-10) (Rammstedt and John, 2007), Perceived Stress Scale (PSS) (Cohen et al., 1983; Lee et al., 2012a), Mindful Attention Awareness Scale (MAAS) (Brown and Ryan, 2003; Jeon et al., 2007), and the Visual Analog scale for Stress perception (VAS). Then, we informed participants regarding the study protocol in more detail, including (a) the mindfulness strategy (i.e., attention focused on the physical sensations of breathing), the mind-wandering strategy (i.e., connecting thoughts as they wish), and the resting-state strategy (Table 1), (b) how to perform the smartphone-based ambulatory training sessions during the next 10 consecutive days, (c) three cognitive tasks, including (i) the *n*-back task (NBT; $n = 3$), consisting of both digits (i.e., 0 to 9) and letters (i.e., *a* to *z*) (Smith and Jonides, 1997), (ii) a facial Emotion Recognition Task (ERT) (Lee et al., 2013), and (iii) the Wisconsin Card Sorting Test (WCST) as a cognitive control test (Grant and Berg, 1948; Monchi et al., 2001), as well as (d) the experimental procedures of the MRI session, which included two non-real-time fMRI (non-rtfMRI) runs, featuring mindfulness and mind-wandering, followed by two rtfMRI-NF runs and one transfer run.

Smartphone-based ambulatory training session

On each of the next 10 consecutive days following the face-to-face interview, an email was sent at 8 am to each participant with a day-specific hyperlink that expired at 3 am the following day. Participants

were required to perform their ambulatory training within this time-frame and received a reminder email at 8 pm if they had not done so by then. During the ambulatory training session, the participants were asked to apply the mindfulness strategy for 5 days and the mind-wandering strategy for the other 5 days in a counter-balanced order (i.e., one strategy per day, alternating; please see the Supplementary Material section, "***Smartphone-based ambulatory training sessions***"). Participants were asked to initiate the daily ambulatory training using their assigned identification and personal codes that were created and given to them on the face-to-face interview day. Participants responded to the Multidimensional Mood State Questionnaire (or the MDMQ, with scales measuring good–bad, awake–tired, and calm–nervous mood; also known as *Multidimensionaler Befindlichkeitsfragebogen*, MDBF, in German) (Steyer et al., 1994; Steyer et al., 1997), the short version of the State Mindfulness Scale (SMS_S) with two questions (Q8 and Q14; Fig. 1b) selected from the original version of the SMS (Tanay and Bernstein, 2013), and the VAS to measure their stress level. The Enterprise Feedback Suite Survey 10.0 (Questback GmbH, Berlin, Germany) was used to build the smartphone-based ambulatory training session with text instructions incorporating the mindfulness and mind-wandering strategies and the collection of questionnaire data, as well as automated invitational and reminder emails to participants.

MRI session

On the MRI experiment day, the participants answered several questionnaires, including the MAAS, MDMQ, SMS, and VAS. Then, the participants were briefed regarding the three cognitive tasks (i.e., ERT, NBT, and WCST). The participants conducted these tasks and, then, were loaded into the MRI scanner in a supine position to acquire MRI data in the following order: two non-real-time fMRI (non-rtfMRI) runs, a field-map, T_1-weighted and T_2-weighted anatomical images, and two rtfMRI-NF runs, followed by one transfer fMRI run (Fig. 1a). One non-rtfMRI run consisted of three 3-minute blocks of mindfulness each followed by one 3-minute block for each of the three cognitive tasks. There was also one 3-minute resting-state block pseudo-randomly positioned between the three mindfulness-cognitive task blocks. The other non-rtfMRI run was the same, except that the mind-wandering rather than the mindfulness strategy was performed. The order of the two non-rtfMRI runs was counter-balanced and

the SMS_S/TPF scores of each of the mindfulness and mind-wandering blocks were obtained. A white cross was fixed in the center of the screen for 30 s between consecutive blocks.

Figure 1b illustrates the task paradigm of the two rtfMRI-NF runs and the one transfer run. During the 300 s neurofeedback period (i.e., from 90 s to 390 s) of each of the two rtfMRI-NF runs, the participants were informed that the height of the thermometer bar with a red-green-blue color scheme would correspond to their level of mindfulness. In addition, they were asked to increase and to maintain the height of the bar while employing the mindfulness strategy. Participants were informed that the current bar represented changes in their brain activity that had taken place approximately 50 s earlier. This lag of approximately 50s was comprised of a 43.2 s temporal window (1.44 s/volume × 30 volumes) to conduct a mediation analysis and an additional 6 s from the hemodynamic response delay to the peak. This window size for mediation analysis in a sliding window framework was determined based on a previous report, in which a window size of 44 s provided a good tradeoff between the ability to resolve the dynamics and the quality of the correlation coefficient estimate used to quantify the dynamic functional connectivity (Allen et al., 2014).

After the neurofeedback period, a 30 s rating period was given to the participants to evaluate their mindfulness scores (i.e., SMS_S) and task-performance feedback (i.e., TPF) scores using a fiber-optic response pad (Current Design, Philadelphia, PA; www.curdes.com), which was placed in their right hand. MR-compatible binocular goggles (NordicNeuroLab, Bergen, Norway) were used to provide visual stimuli. During the 300 s period of the subsequent transfer run, a white cross was displayed in the center of a black screen for participants to fixate on, and participants were asked to deploy their learned strategy from the rtfMRI-NF runs to enhance their level of mindfulness without the thermometer bar. Then, a 30 s rating period was given to the participants to evaluate their mindfulness score and task-performance feedback score. Electroencephalography (EEG) data were also acquired simultaneously with fMRI. During the debriefing session that followed the MRI session (i.e., the post-MRI period), the participants replied to a battery of questionnaires (i.e., the MDMQ, SMS, and

VAS) and again performed the three cognitive tasks (i.e., the ERT, NBT, and WCST) as in the pre-MRI period.

Participants

Sixty right-handed, healthy male volunteers (mean ± standard deviation (STD); age = 25.1 ± 2.9 years) participated in this study. Each participant was randomly assigned to either the experimental or the control group based on a block randomization method and each experimental subject was paired with one control subject (see details in the "***Counterbalancing the task paradigm and randomization procedure to allocate participants to either the experimental or control group***" section of the Supplementary Materials). The participants were blinded to the group assignment and were informed about only the experimental paradigm and the tasks to deploy in the MRI session. All the participants were subject to the non-rtfMRI runs, followed by the rtfMRI-NF runs and one transfer run. The participants in the experimental group were given contingent neurofeedback information derived from their own brain signals, whereas the participants in the control group were given non-contingent neurofeedback information, which originated from their paired subject in the experimental group.

Imaging parameters

A 3-T Siemens Tim-Trio scanner with a 12-channel head coil (Erlangen, Germany) was used to acquire the MRI data. The standard gradient-echo echo-planar-imaging (EPI) pulse sequence was used for fMRI data acquisition with the following parameters: multiband factor of two using in-plane multiband GeneRalized Autocalibrating Partial Parallel Acquisition acceleration (or, GRAPPA 2); time of repetition (TR) = 1440 ms; time of echo (TE) = 30 ms; field-of-view (FoV) = 192 × 192 cm^2; voxel size = 3 × 3 × 3 mm^3; flip angle (FA) = 71°; 50 axial slices with no gap. The 3D magnetization-prepared rapid gradient-echo (MPRAGE) pulse sequence was used to acquire a T_1-weighted image (TR/TE = 1900/2.52 ms; FoV = 256 × 256 cm^2; voxel size = 1 × 1 × 1 mm^3; FA = 9°; 176 sagittal slices with no gap). The 3D MPRAGE was also used to acquire the T_2-weighted image (TR/TE = 3000/402 ms; FoV = 256 × 256 cm^2; voxel size = 1 × 1 × 1 mm^3; 176 sagittal slices with no gap). Then, the field-map was obtained (TR = 800 ms; TE_1 = 10 ms; TE_2 = 13.94 ms; FoV = 240 × 240 cm^2; voxel size = 1.9 × 1.9 ×

4.0 mm^3; FA = 25°; 36 sagittal slices with no gap). During the fMRI runs, respiration and pulse oximeter signals were simultaneously recorded using the scanner's built-in wireless pneumatic belt, which was positioned at the level of the abdomen, and a fingertip pulse oximeter placed on the left index finger, respectively.

Mediation analysis model of the triple network to extract the functional feature of mindfulness

Figure 2a illustrates the mediation analysis model (MacKinnon, 2008) using the triple networks, in which BOLD signals from the SN are represented by the independent variable $x(t)$ (because of the interoceptive function of the SN, which would be induced by our mindfulness strategy based on focused attention to the physical sensations of breathing). BOLD signals from the DMN are represented by the dependent variable $y(t)$ (because of the self-referential function of the DMN, which would be related to mindfulness status). In addition, BOLD signals from the CEN were assigned as the mediator variable $m(t)$ (because of the goal-oriented cognitive function of the CEN, which would be induced from effort related to the external thermometer bar control). The partial regression coefficient (i.e., slope) value between the SN and the DMN, with the CEN as a mediator (i.e., c' in Fig. 2a), was calculated using Pearson's correlation coefficients between (a) the SN and the DMN (i.e., r_{xy}), (b) the SN and the CEN (i.e., r_{xm}), and (c) the CEN and the DMN (i.e., r_{my}) as follows (see Appendix B for more details):

$$c' = \frac{(r_{xy} - r_{xm} r_{my})}{(1 - r_{xm}^2)} \frac{\sigma_y}{\sigma_x}, \quad (1)$$

where σ_x and σ_y were the standard deviations of the signals from the SN and the DMN, respectively. In the triple networks framework, our model of mindfulness based on the mediation analysis was also compared with alternative models using Pearson's correlation analysis between a pair of triple networks and partial correlation analysis across the triple networks (Figs. 2b and 2c; Appendix A and C for a mathematical comparison).

Regions-of-interest definition of the triple networks

Regions-of-interest (ROIs) within the triple networks were initialized from a term-based meta-analysis using the Neurosynth repository (neurosynth.org) employing the reverse inference option with a false

discovery rate, or FDR $p < 0.01$ (Yarkoni et al., 2011). The keywords used were the "frontoparietal network" for the CEN (since there is no meta-analysis map for the "central executive network"), the "default network" for the DMN, and the "salience network" for the SN. Then, the obtained ROIs in Montreal neurological institute (MNI) space were warped into the individual subject's EPI space (Fig. 3a). This was achieved by applying a "warping matrix", an inverse of the transformation matrix to normalize the subject's first EPI volume to the EPI template in the MNI space used by the statistical parametric mapping software toolbox (SPM8; Lee et al., 2008). These initial ROIs of the triple networks in each subject's EPI space were further fine-tuned for each individual using the estimated triple networks by applying spatial independent component analysis (McKeown et al., 1998b) to the two 3-minute resting-state blocks in the two non-rtfMRI runs (as exemplified in Fig. 3b and 3c; see details in the "***Fine-tuning of regions-of-interest of the triple networks using individual fMRI data***" section of the Supplementary Materials). Figure 3d shows the group-level fine-tuned ROIs obtained from the one-sample *t*-test across all 60 participants (FDR $p < 0.01$, with a minimum of 10 connected voxels).

Two real-time fMRI neurofeedback runs and one transfer run: online analysis

Preprocessing

The fMRI volume series from both the two rtfMRI-NF runs and the one transfer run were preprocessed using SPM8. The preprocessing began at 40 s after the cross-fixation period and proceeded in the following order: (a) realignment to the first fMRI volume; (b) de-trending; (c) de-spiking (i.e., if the average BOLD intensity across the whole-brain of the current fMRI volume was greater than 110% or lower than 90% of the mean of the average BOLD intensities across previous fMRI volumes, the current fMRI volume was replaced by the fMRI volume of the previous TR) (Garrison et al., 2013); (d) motion censoring (i.e., if the frame-wise displacement, or FD of the current fMRI volume compared with the first fMRI volume was greater than 0.5, the current fMRI volume was replaced by the fMRI volume of the previous TR) (Power et al., 2014); (e) spatial smoothing with an 8 mm full width at half maximum Gaussian kernel; (f) physiological noise correction using the aCompCor method with five principal components (PCs) from the cerebrospinal fluid (CSF) and white matter (WM) regions, respectively (Behzadi et al., 2007). In detail, a priori maps of the WM and CSF regions in MNI space, available in

SPM8, were registered into individual native EPI space using the warping matrix. Then, the voxels in the warped a priori maps with a probability greater than 0.7 for the CSF or 0.9 for the WM were used to extract the PCs of the CSF and WM, respectively; (g) nuisance regression applying three translational and three rotational head motion parameters; and (h) bandpass filtering from 0.01 to 0.1 Hz (Kilpatrick et al., 2011; Su et al., 2016) using a fast Fourier transform (Song et al., 2011).

Neurofeedback information

The ROIs of the triple networks were realigned to the first volume in the rtfMRI-NF run, and voxels belonging to the WM and CSF (defined during the aCompCor step) were excluded. Beginning from 90 s (Fig. 1b), the most recent 30 volumes (i.e., spanning 43.2 s), including the volume at the current TR, were subjected to mediation analysis to calculate the neurofeedback signal (i.e., c'). The neurofeedback signal in the subsequent TR was calculated by advancing by one TR, based on a sliding window approach (Allen et al., 2014). In detail, the average BOLD signals across voxels in each ROI of the triple networks were calculated and then re-scaled to have a mean of 100. Then, the average BOLD signals of the SN (i.e., $x(t)$) and the CEN (i.e., $m(t)$) were normalized between 0 and 1 by subtracting the minimum value of the BOLD signal followed by dividing by the difference between the maximum and minimum of the BOLD signal (i.e., $\frac{x(t)-\min(x(t))}{\max(x(t))-\min(x(t))}$ and $\frac{m(t)-\min(m(t))}{\max(m(t))-\min(m(t))}$, where min (·) and max(·) are the functions calculating the minimum and maximum values, respectively). These normalized signals, along with a vector of ones to estimate the bias term b_1, were used as regressors in the general linear model framework (see "***Appendix B***" for details). Since $y(t)$ was re-scaled to have a mean of 100, the re-scaled $y(t)$ represents the percentage signal change compared to the mean. For instance, if the mean of $y(t)$ (i.e., baseline BOLD intensity of $y(t)$) was originally 1000 and $y(t_i)$ = 1010 at time point t_i, then the percentage signal change of $y(t_i)$ = (1010 – 1000)/1000×100 = 1%. Now, when we scaled $y(t)$ to have a mean of 100 by dividing $y(t)$ by 10, then $y(t_i)$ = 101. The bias term, b_1 would estimate a mean of 100 of the re-scaled $y(t)$, and thus, $y(t) - b_1 = c'x(t) + bm(t) + e_1(t)$, where the left side of the equation (i.e., $y(t) - b_1$) becomes the percentage (%) signal change in $y(t)$. Thus, the regression coefficients c' as well as b denote the percentage signal changes for each of the

$x(t)$ and $m(t)$ regressors (which were normalized between 0 and 1). c' was used for the neurofeedback interface, presented as a thermometer bar. To set the maximum and minimum range of the bar, a pilot study was conducted with three subjects (data not shown), and the highest and lowest levels of the thermometer bar were set to c' values of + 0.5 and – 0.5, respectively.

Software toolbox

Our in-house software toolbox (implemented in a MATLAB environment; version R2016b), which has been used in our previous rtfMRI-NF studies (Kim et al., 2015a; Lee et al., 2012c; Lee et al., 2008; Lee et al., 2009; Yoo et al., 2007; Yoo et al., 2008), was updated for the present study. The rtfMRI-NF toolbox was executed on a desktop computer (Intel Core i7-3770 CPU @ 3.40 GHz, 16-GB RAM, 256-GB SSD hard drive, Windows 7) connected to an MRI console computer via TCP/IP using the "net use" command. Thereby, the raw fMRI volumes that were reconstructed in the MRI console computer became available in the desktop computer. Then, the fMRI volumes of the two rtfMRI-NF runs on the desktop computer were used to generate neurofeedback information obtained from the mediation analysis. The time delay from the acquisition of a raw fMRI volume to the presentation of neurofeedback information (i.e., c') was less than a TR.

Offline analysis

The main purpose of the ambulatory training was to provide an opportunity for meditation-naïve participants to become familiar with the task strategies (Table 1). However, potential group difference may be caused by the smartphone-based ambulatory training, such as in overall behavioral scores and in their improvements over time. Thus, this possibility and a potential interaction with the rtfMRI-NF training were investigated (please refer to the section "***Analysis of the behavioral data obtained from the smartphone-based ambulatory training***" in the Supplementary Materials for details).

The participants' rating scores collected during the MRI session were used to evaluate the two rtfMRI-NF runs and one transfer run. Compared with the online analysis by applying the aCompCor

method, potential physiological artifacts present in the BOLD signals could be further reduced by applying the RETROICOR method using pulse oximeter and respiration belt signals (Glover et al., 2000). In detail, the two phasic signals extracted from the respiration belt and pulse oximeter signals were down-sampled to have the same temporal resolution as the BOLD signals (i.e., TR) using the Physiological Log Extraction for Modeling (PhLEM) Toolbox (Verstynen and Deshpande, 2011). Then, the least-squares algorithm was used to regress these physiological data out of the BOLD signals (Behzadi et al., 2007; Chai et al., 2012; Kim et al., 2015a; Kim et al., 2015b; Kim et al., 2013; Lee et al., 2012b; Song et al., 2011).

A two-sample *t*-test was used to compare cardiac and respiratory cycles between the experimental and control groups. Because of head motion (i.e., FD > 0.5 for longer than half of the mindfulness period in any of the rtfMRI-NF runs or the transfer run), eight participants were excluded from further analysis (two subjects in the experimental group and their matched subjects in the control group; two subjects in the control group and their matched subjects in the experimental group). Table S2 summarizes their sociodemographic information and psychological traits as well as head motions. Thus, 52 participants (26 participants per group) were included in the analysis of this study.

Next, the regression coefficient levels in the mediation analysis model of the triple networks (i.e., a, b, and c') calculated from the offline and online analyses were compared. A correlation analysis was applied to the average of the two mindfulness scores (i.e., SMS_S) and the task-performance feedback score to evaluate the possibility of whether our neurofeedback information (i.e., c') reflected the level of mindfulness. To remove any potential residual effects from a rehearsal during the instruction period of the mindfulness strategy (i.e., 75 s–85 s) before the mindfulness task-period began, for this correlation analysis, the average c' value across all the 43.2 s windows was calculated by excluding the 43.2 s (i.e., 30 volumes) at the beginning of the 300 s task-period. As such, alternative regression coefficient levels (i.e., a or b) may represent the level of mindfulness, and this possibility was also investigated using average mindfulness scores and task-performance feedback scores in the correlation analysis with their corresponding regression coefficient levels. Additionally a bootstrapping method

has been used to conduct a statistical analysis of the difference in correlations (e.g., "c' vs. mindfulness scores" – "b vs. mindfulness scores", or CC(c', SMS_S) – CC(b, SMS_S) to remove potential bias from the mediation effect b from the CEN to the DMN) (Terhune et al., 2014) (Table 3). Also investigated was (a) a potential association between the amount of mediation (i.e., ab) and the mindfulness/task-performance scores and (b) whether the amount of mediation was equivalent between the two groups when the direct effect (i.e., c') was compared between them. The potential association between the total effect (i.e., c; Fig. 2b) and mindfulness/task-performance scores has also been investigated. Moreover, the possibility that the FC levels calculated from Pearson's correlation analysis or partial correlation analysis represented the level of mindfulness was also investigated. Potential outliers in the behavioral data as well as the regression coefficients (i.e., slopes) from the mediation analysis and simple/partial correlation coefficients were identified (see "***Definition of outliers based on median absolute deviation (MAD)***" for details in the Supplementary Materials) and subsequently removed from the correlation analysis between the behavioral data and the brain data.

Control analyses

Correlation analysis between paired participants for each of the reported mindfulness/task-performance scores and c' values

In the rtfMRI-NF training, participants were asked to increase the thermometer bar (i.e., c') while deploying the mindfulness strategy based on attention to the physical sensation of breathing. Subsequently, correlations between the c' values and the mindfulness/task-performance scores were investigated to evaluate the efficacy of the rtfMRI-NF training. The possibility that this "dual-task" setting might have resulted in the significant positive association between c' and the mindfulness/task-performance scores needs to be addressed. To evaluate this, we conducted control analyses to determine any (a) correlation between paired participants (who watched the same thermometer bar) for each of the reported mindfulness/task-performance scores and c' values; (b) association between the mindfulness scores and potentially alternative mindfulness-related features of the brain such as activations in the triple networks; (c) association between cardiac/respiratory measurements and brain

data or mindfulness/task-performance scores. To evaluate possibility (a), correlation analyses of the c', SMS_S, and TPF scores across the paired participants were conducted using the data obtained from the rtfMRI-NF runs and the transfer run. Evaluations of the possibilities of (b) and (c) are described in the following sub-sections.

Percentage blood-oxygenation-level-dependent (BOLD) signal changes vs. mindfulness

It may be possible that activations in one or more of the ROIs in the triple networks may have changed in the rtfMRI-NF setting and become associated with mindfulness. To evaluate this possibility, a correlation analysis was conducted between the activation levels in the ROIs and the mindfulness/task-performance scores. The candidate ROIs of the sub-regions of the triple networks were defined from the group-level ROIs of the triple networks (Fig. 3d). In detail, the SN was sub-divided into the dorsal anterior cingulate cortex of the SN (SN_{dACC}) and the bilateral anterior insular cortices of the SN (SN_{INS}) (Seeley et al., 2007) (Fig. S8). The DMN was sub-divided into the anterior part of the DMN (aDMN), which includes the medial prefrontal cortex, or mPFC, and the posterior part of the DMN (pDMN), which includes the PCC ($pDMN_{PCC}$) and the bilateral inferior parietal lobule of the pDMN ($pDMN_{IPL}$) (Kim and Lee, 2011) (Fig. 10). The CEN was sub-divided into the frontal part of the CEN (i.e., the bilateral frontal area of the CEN (CEN_F)) and bilateral parietal area of the CEN (CEN_P) (Menon, 2011) (Fig. S8). These sub-regions of each of the triple networks were defined using the Xjview software toolbox (www.alivelearn.net/xjview). In addition, specific seed regions of the DMN such as the mPFC (MNI coordinate: [−6, 52, −2] mm) and PCC ([−8, −56, 26] mm) consisting of spheres 9 mm in radius have also been employed as ROIs (Brewer et al., 2011; Garrison et al., 2013).

The raw fMRI volumes were preprocessed according to the following sequence: realignment to the first EPI volume, detrending, spatial smoothing with an 8 mm full width at half maximum Gaussian kernel, physiological noise correction using each of the 5 PCs from the CSF and WM, nuisance regression using six motion parameters, and band-pass filtering between 0.01 and 0.1 Hz. The percentage BOLD (pBOLD) signals during the task-period (i.e., 97.2 s – 390 s after the exclusion of 5 volumes from task onset to remove any confounding effect from the rehearsal phase spanning 75 s – 85

s) were calculated from the preprocessed data using a baseline BOLD intensity defined as the average BOLD intensity between 10 - 40 s during the first cross-fixation period (Fig. 1b). Then, average pBOLD intensity was calculated across the task-period after excluding the pBOLD intensity outliers (see the Supplementary Material section, "***Definition of outliers based on median absolute deviation (MAD)***" for details) and excluding the EPI volumes featuring severe head motion (FD score > 0.5).

Cardiac/respiratory cycles vs. regression coefficients in the mediation analysis and/or mindfulness/task-performance scores

The possibility of whether the cardiac/respiratory cycles during the training may have contributed to the changes in (a) the regression coefficients from the mediation analysis and/or (b) the mindfulness scores and task-performance feedback scores was investigated. The cardiac (beats/minute) and respiratory (breaths/minute) cycles were extracted using the PhLEM toolbox.

Effective connectivity of the triple networks

Our hypothesized model suggested that interoceptive perception in the SN may induce mindfulness states in the DMN, mediated by the CEN. However, it is still unclear whether the interoceptive perception caused the mindfulness status or whether, conversely, the mindfulness status itself caused the enhancement in interoceptive perception. Another possibility is that the triple networks may have been causally linked to each other and that this causal connection may have been characterized differently based on both the type of training run (i.e., rtfMRI-NF run vs. transfer run) and the type of the NF information provided (i.e., contingent for the experimental group vs. non-contingent for the control group). To investigate this possibility, spectral dynamic causal modeling (spDCM) in SPM12 (www.fil.ion.ucl.ac.uk/spm/software/spm12) that has been gainfully applied to the resting-state fMRI data was used (Friston et al., 2014). The detailed analysis step can be found in the Supplementary Materials ("***Effective connectivity among the triple networks using spectral dynamic causal modeling (spDCM)***").

Results

Data from subjective ratings and raw fMRI

The completion ratio of the smartphone-based ambulatory training sessions (i.e., 86.67 % ± 16.47 for the experimental group vs. 87.00 % ± 12.64 for the control group) did not statistically differ between the two groups ($p = 0.93$; Table S1). The results from the ambulatory training suggested that there was no main effect of group, sequence-of-condition for mindfulness and mind-wandering strategies, or their interaction with the rtfMRI-NF training in (a) the PSS, MDMQ, SMS, VAS, and TPF scores obtained on the last day of the ambulatory training (Fig. S1d) and (b) the MDMQ, SMS, and VAS scores obtained in the pre-MRI session (Fig. S2) (see "***Data from smartphone-based ambulatory training***" for details in the Supplementary Materials).

Figure 4a shows that, based on the MDMQ results, mood changed differently between the two groups in the MRI session. They both showed significantly higher levels of mindfulness (measured by the SMS; $p < 10^{-3}$, obtained from a paired *t*-test with the *p*-value corrected from 10,000 random permutations) after the MRI session than before. There were no significant changes in participant stress levels. Figure 4b shows that there were no significant differences in the mindfulness or task-performance scores across runs or across groups. In addition, Figure 4c shows that the regression coefficient levels obtained from the online and offline analyses did not differ.

The cardiac cycle (i.e., mean ± STD; 62.6 ± 8.6 beats per minute for the experimental group and 64.5 ± 9.8 for the control group, $p = 0.26$ from the two-sample *t*-test) and respiratory cycle (11.6 ± 3.9 breaths per minute for the experimental group and 11.5 ± 4.8 for the control group, $p = 0.87$) did not statistically differ between the two groups. The average (± STD) FD values of head motion from the resting-state blocks for each of the two non-rtfMRI runs were 0.11 (± 0.05) for the first run and 0.12 (± 0.08) for the second run. There was no volume for which the FD value was above 0.5, and the FD values across the rtfMRI-NF runs and the transfer run did not significantly differ between the two

groups (i.e., 0.13 ± 0.08 for the experimental group and 0.12 ± 0.07 for the control group; $p = 0.88$ from the two-sample *t*-test).

Regression coefficient feature of mindfulness in the mediation analysis framework

Figure 5a shows the line plots of the average c' level, with standard errors in the shaded areas. Overall, the regression coefficient (i.e., slope) levels of the experimental group were significantly greater than those of the control group at several time-points (i.e., those marked by an asterisk *; paired difference was also plotted in gray). Average slope levels (i.e., c' levels across the 300 s of each run did not statistically differ between the two groups, although the mean slope level of the experimental group was higher than that of the control group ($p = 0.32$, 0.14, and 0.58 for the rtfMRI-NF run#01, #02, and transfer run, respectively). Figure 5b shows that the neurofeedback signal (i.e., c') was significantly correlated with the mindfulness and task-performance feedback scores in the rtfMRI-NF runs, only in the experimental group. Figure S3 shows that those positive correlations from the rtfMRI-NF runs were retained even after the subtraction of the respective correlations between the mediation effect (i.e., b) and the mindfulness scores and task-performance feedback scores. The corresponding 95% CIs were [0.05, 0.88] for the correlation with mindfulness scores and [0.10, 0.92] for the correlation with the task-performance feedback scores.

Regression coefficient levels from other pairs of the triple networks in the mediation analysis framework

Figure 6a shows that there was a significant positive correlation between the regression coefficient (i.e., slope) from the SN to the CEN (i.e., a) and the task-performance feedback scores for the control group. Figure 6b shows that the slope levels from the CEN to the DMN (i.e., b) of the control group in the rtfMRI-NF runs presented weakly suggestive and significantly positive correlations with the mindfulness and task-performance feedback scores, respectively. On the other hand, the slope (i.e., b) and the task-performance feedback scores of the experimental group showed a weakly suggestive negative correlation in the rtfMRI-NF runs. Figure 7a shows that the mediation effect ab values

presented significant positive correlations with the mindfulness scores and task-performance feedback scores in the rtfMRI-NF runs only for the control group. In the time plots, the mediation effect, ab values did not significantly differ between two groups, particularly when the direct effect, c' values, significantly differed between two groups (small square boxes). Figure 7b shows that the slope, c (i.e., the total effect from the SN to the DMN) presented significant correlation and suggestive positive correlation with the mindfulness scores and task-performance feedback scores, respectively, in the rtfMRI-NF runs of the experimental group. However, the time plots show that the time points that featured significantly greater intensities from the experimental group than the control group were more associated with the direct effect (i.e., c'; rectangular box) than the total effect (i.e., c; asterisk). Also, the statistical significance was stronger when considering c' (i.e., $p = 0.007$ with the mindfulness scores and $p = 0.001$ with the task-performance scores; Fig. 5b) than when considering c (i.e., $p = 0.04$ and $p = 0.01$; Fig. 7b).

FC levels from Pearson's correlation and partial correlation analyses

Figure 8a shows that the FC levels (from simple correlation coefficients) between the SN and the DMN resulted in suggestive positive correlations with the mindfulness scores in both the rtfMRI-NF and transfer runs, but only from the experimental group. In the time plots, the time-points that showed greater FC levels for the experimental group than the control group became scarce in the second rtfMRI-NF run (cf., Fig. 5a).

Figure 8b shows that the FC levels (from partial correlation coefficients) between the SN and the DMN, with the adjusting variable from the CEN, presented significant and suggestive positive correlation with the mindfulness scores in both the rtfMRI-NF runs and the transfer run only with the experimental group. The corresponding statistical significance of the correlation coefficient in the rtfMRI-NF run ($p = 0.002$) was slightly greater than that of the mediation analysis ($p = 0.007$; Fig. 5b). However, the time-points that showed statistically greater ($p < 0.05$) FC levels (i.e., $r_{SN,DMN \cdot CEN}$) from the experimental group than the control group were fewer compared to the time plots of c' (cf., Fig. 5a).

Results of the control analyses

Figure 9 shows that there was no meaningful correlation of the c' values, mindfulness scores, or task-performance feedback scores between the paired participants across the two groups during both the rtfMRI-NF and transfer runs. Figure 10 shows that there were significant correlations between the pBOLD intensities of the sub-regions of the DMN and mindfulness/task-performance scores. Particularly, it is notable that the significant negative correlations between the aDMN/mPFC activations and the mindfulness scores in the rtfMRI-NF runs are only from the experimental group. Also, the negative correlations between the PCC activations and the mindfulness scores, which were potentially weakly suggestive in the rtfMRI-NF runs, became significant in the transfer run only with the experimental group. The average activations during the task-period in the PCC area for the experimental group (mean $\pm$ STD; –0.012 $\pm$ 0.067 in the rtfMRI-NF run#01 and –0.014 $\pm$ 0.073 in the rtfMRI-NF run#02) were slightly lower compared to those for the control group (–0.009 $\pm$ 0.060 and 0.003 $\pm$ 0.006) during the rtfMRI-NF runs. On the other hand, the activation levels in the PCC for the control group (–0.010 $\pm$ 0.086) were slightly lower than those from the experimental group (–0.005 $\pm$ 0.081) during the transfer run. However, these differences were not statistically significant between the two groups. Figure S8 shows that there were weakly suggestive and potentially weakly suggestive correlations between the activations in the sub-regions of the SN and CEN and mindfulness/task-performance scores, but there was no significant correlation. Figure S9 shows example time plots of the PCC activations of a pair of participants who reported high average mindfulness scores across the two rtfMRI-NF runs and one transfer run (8.3 $\pm$ 0.3 from the participant in the experimental group, 7.7 $\pm$ 0.6 from the participant in the control group). Figure 11 shows that the cardiac cycles showed a suggestive negative correlation with slope a, a significant negative correlation with slope b, and a weakly suggestive positive correlation with the mindfulness scores, but only from the experimental group during the rtfMRI-NF runs. There was no meaningful correlation under other conditions such as when using the respiratory cycles or with the control group.

Effective connectivity of the triple networks

The fully-connected model with bi-directional effective connectivity between the pairs within the triple networks was selected as an optimal model for both the rtfMRI-NF and the transfer runs. Figures 12(a-b) show that the experimental group presented significant positive effective connectivity (i) from the CEN and DMN to the SN in the rtfMRI-runs and (ii) from the SN and CEN to the DMN in the transfer run. The self-connection within the DMN showed significant negative correlation with the mindfulness scores only during the rtfMRI-NF runs. Figures 12(c-d) show that the control group presented significant positive effective connectivity (i) from the CEN to the SN in the rtfMRI-NF runs and (ii) from the CEN to the DMN in the transfer run. The mindfulness scores showed weakly suggestive correlation or suggestive negative correlation with the self-connections within the SN in the rtfMRI-NF runs and within the CEN in the transfer run, respectively, for the control group. The task-performance scores showed weakly suggestive positive correlation with the inter-network connection from the CEN to the DMN in the transfer run for the control group.

Discussion

Summary

In this study, we demonstrated that the partial regression coefficient level (i.e., direct effect, c') from the SN to the DMN, mediated by the CEN in the mediation analysis framework, appears to be one of the potential features of mindfulness in the rtfMRI-NF setting. The validity of this regression coefficient (i.e., slope) feature was further evaluated from its statistically significant positive association with the mindfulness and task-performance scores independently measured after each rtfMRI-NF run and transfer run. These positive correlations between c' and the mindfulness scores (i.e., CC(c', SMS_S)) and between c' and the task-performance feedback scores (i.e., CC(c', TPF)) remained significant even after the correlation coefficients between b and SMS_S (i.e., CC(b, SMS_S)) and TPF (i.e., CC(b, TPF)) were subtracted. The regression coefficient (i.e., total effect, c) from the SN to the DMN also showed significant correlation with the mindfulness scores and task-performance feedback scores in our rtfMRI-NF runs. It is notable, however, that the level of statistical significance when considering the

direct effect from the SN to the DMN (c'; by excluding the indirect/mediation effect via the CEN) was stronger than that when considering the total effect from the SN to the DMN (c; Fig. 7b). This suggests that the efficacy of our rtfMRI-NF training of mindfulness was better explained in terms of c' which excludes the mediating effect via the CEN (i.e., ab) from the total effect from the SN to the DMN (i.e., c) and this supports our hypothesis that c' is a potential mindfulness feature in our rtfMRI-NF setting. In addition, the participants were able to enhance this functional feature of mindfulness when the partial regression coefficient feature was used as contingent neurofeedback information. Furthermore, the regression coefficient levels from the other pairings of the triple networks did not appear to reflect the mindfulness level. In addition, enhancement of the FC level was not evident during the rtfMRI-NF runs when the FC levels were calculated either from Pearson's correlation analysis (between the SN and the DMN) or partial correlation analysis (between the SN and the DMN, as adjusted by the CEN).

Changes in the subjective ratings of mindfulness and task-performance scores in the MRI session

Interestingly, it appeared that participant mood was changed after the MRI session (i.e., significant decreases in good–bad and awake–tired moods for the control group and a weakly suggestive increase in the calm–nervous mood for the experimental group; Fig 4a). This may be because of the effect of having the two rtfMRI-NF runs with contingent or non-contingent NF information, which was the only difference between the two groups. There was no significant group-based difference between the mindfulness or task-performance scores obtained from the rtfMRI-NF runs and the transfer run. However, the mindfulness and task-performance scores were significantly correlated with the regression coefficient levels from the SN to the DMN, as mediated by the CEN, but for the experimental group only. During the debriefing session, approximately half of the participants gave a verbal or written assessment of their performance during the rtfMRI-NF runs. Twelve of these subjects from the experimental group reported that they noticed that the thermometer bar had changed as they expected, and three subjects in the group reported that it had not changed as they expected. On the other hand, in the control group ten subjects reported that the thermometer bar did not change as they had expected,

although they reported that they had managed to increase the bar by enhancing their mindfulness level, and two subjects reported that the thermometer bar had changed as they expected.

Potential confounding physiological artifacts due to mindfulness strategy

In our study, focused attention on the physical sensations of breathing was adopted as a mindfulness strategy, which may confound the BOLD signal (Birn et al., 2008; Raj et al., 2001). Thus, we made a significant effort to reduce potential respiration artifacts in the BOLD signal by using aCompCor-based physiological noise removal in the online analysis and additionally RETROICOR in the offline analysis (Behzadi et al., 2007; Glover et al., 2000). The resulting regression coefficient (i.e., slope) levels obtained from the online analysis were comparable to those obtained from the offline analysis (Fig. 4c). This indicates that the physiological artifacts in the BOLD signal were still sufficiently reduced when slope levels were calculated during the online analysis. In Fig. 4c, the fact that the slope levels between the SN and the CEN (i.e., a) were greater than those between the SN and the DMN (i.e., c') and those between the CEN and the DMN (i.e., b) is in accordance with previous studies (Farb et al., 2007; Mooneyham et al., 2016). For example, in mindfulness the CEN integrates the moment-to-moment input from a variety of somatic and sensory systems received in the SN by conscious executive processing (Mooneyham et al., 2016).

Correlation between alternative regression coefficient levels across the triple networks and subjective ratings

In our mediation analysis framework, the regression coefficient (i.e., slope) levels between the CEN and the DMN showed weakly suggestive and significant positive correlations with mindfulness and task-performance feedback scores, respectively, for the control group in the rtfMRI-NF runs (Fig 6b). Also, the mediation effect ab consistently showed significant positive correlation with the mindfulness/task-performance scores in only the rtfMRI-NF runs of the control group (Fig. 7a). Moreover, it is notable that this significant positive correlation using the overall mediation effect ab was stronger than the positive correlation obtained when using either a or b alone (cf., Fig. 7a and Fig.

6). This finding indicates that the participants in the control group reported mindfulness and task-performance scores based on how much they "controlled" the thermometer bar. This is likely because the CEN, which has been associated with goal-oriented cognition (Beaty et al., 2015; Christoff et al., 2016; Mooneyham et al., 2016; Sridharan et al., 2008; Uddin, 2015), elevated neuronal activation when the participants tried to control the level of the bar. In turn, this may have induced a greater mindfulness status, which was reflected in the self-referential processing of the DMN (Hasenkamp and Barsalou, 2012; Mooneyham et al., 2016; Wells et al., 2013). On the other hand, the task-performance scores of the participants in the experimental group were inversely correlated with the slope levels between the CEN and the DMN in the rtfMRI-NF runs (Fig 6b). This indicates that the participants in the experimental group rated low task-performance scores when they tried to control the level of the bar.

Time-course of regression coefficient from mediation analysis compared with FC from the Pearson's and partial correlation analyses

Increased FC levels between the SN and the DMN were observed in participants with relatively short mindfulness training experience (Mooneyham et al., 2016). Based on the results of our mediation analysis, time-points that showed statistically greater slope levels from the experimental group than the control group were more evident compared to when using Pearson's correlation or partial correlation analyses (Fig. 5 vs. Fig. 8). These results indicate that our analysis model of the mediation of the triple networks may be better suited to describe our experimental data than the two alternative analysis models. Interestingly, the significantly increased slope levels between the SN and the DMN, as mediated by the CEN, in the transfer run at the beginning of the run from 90 s to about 105 s were more noticeable for the experimental group than the control group (Fig. 5a). This may be because of the rehearsal of the mindfulness strategy just before the 300 s task-period (Fig. 1b), indicating that only the participants from the experimental group had successfully learned how to employ the mindfulness strategy with the assistance of the two rtfMRI-NF runs.

Alternative mediation analysis model of the triple networks in comparison with Pearson's correlation and partial correlation analyses

Although our results seem to indicate that our hypothesized regression coefficient (i.e., slope) from the SN to the DMN, as mediated by the CEN, is a strong candidate for the feature of mindfulness, it is also worth noting that the slope level from the DMN to the SN, as mediated by the CEN, has also shown weakly suggestive positive correlations with the mindfulness/task-performance scores in the rtfMRI-NF runs only in the experimental group (Fig. S4). This slope level of the experimental group also showed a potentially weakly suggestive positive correlation with the mindfulness scores in the transfer run. Interestingly, for the experimental group the regression coefficients from the DMN to the CEN presented weakly suggestive negative correlations with the mindfulness/task-performance scores (Fig. S5b), whereas for the control group the regression coefficients from the CEN to the DMN showed weakly positive correlations with the mindfulness/task-performance scores (Fig. S5). It is less likely that slope levels between the SN and the CEN, as mediated by the DMN, would be related to mindfulness features (Fig. S6). The correlation analyses using FC levels from alternative pairs of the triple networks as obtained by Pearson's correlation or partial correlation analyses and mindfulness scores did not show significant associations, indicating that these features may not be well suited to our experimental data (Fig. S7).

Control analyses to investigate the effect of a potential "dual-task" experimental setup

Correlation analysis between paired participants for each of the reported mindfulness/task-performance scores and c' values

Our adopted paradigm may be vulnerable to a potential "dual-effect", in that participants were told to increase the neurofeedback signal c' while enhancing their mindfulness status and subsequently the efficacy of our rtfMRI-NF training was evaluated based on the correlation between c' and mindfulness scores. We observed that (a) there was no meaningful correlation of the mindfulness scores, task-performance feedback scores or c' values between the paired participants across the two groups (Fig. 9) and (b) the activations in the DMN areas also showed a significant negative correlation with mindfulness scores only in the experimental group (Fig. 10). These observations suggest the possibility

of modulation of the mindfulness related features of the brain other than that represented by the regression coefficient (i.e., c') from the SN to the DMN, as mediated by the CEN, possibly including the activations in the mPFC and/or PCC.

Association between activations in the default-mode network and mindfulness scores

It is interesting to note that associations between the activations in the DMN and the mindfulness/task-performance scores were significant only for the experimental group, although the statistical significance was less strong than the degree of association between the regression coefficients (i.e., slopes; c') and mindfulness/task-performance scores. In detail, the aDMN and mPFC showed significant negative correlation in the rtfMRI-neurofeedback runs only, whereas the PCC showed significant negative correlation in the transfer run. This might be due to the slightly different functions of the sub-regions of the DMN (Brewer et al., 2011; Garrison et al., 2013; Posner et al., 2007; Tang et al., 2015). More specifically, the aDMN including the mPFC has been reported to be associated with the self-referential processing related to attentional control (Farb et al., 2007; Ives-Deliperi et al., 2011) and the regulation of internal/external attentional sources (Brewer et al., 2013; Burgess et al., 2007; Davey et al., 2016; Scheibner et al., 2017). In our study, the mPFC might have been dominantly involved in the rtfMRI-NF runs given the constantly presented thermometer bar. On the other hand, the PCC activations might have been involved with mindfulness in the transfer run, where there was no neurofeedback information. In fact, Scheibner et al. (2017) reported strong deactivation of the PCC during internal attention (mindfulness to breathing sensations) compared to external attention (i.e., mindfulness to external sounds), and perhaps this difference may reflect the internal self-referential processing role of the PCC. Despite these findings, it is still unclear whether (a) the changes in our neurofeedback information (i.e., the c' slope value) were driven by the activation changes from a single ROI or multiple ROIs in the triple networks and/or (b) the changes in our neurofeedback information drove the activation changes of the ROIs, so future studies of these possibilities are warranted.

Cardiac/respiratory cycles vs. regression coefficients in the mediation analysis and/or mindfulness/task-performance scores

Participants in the experimental group may have enhanced their mindfulness status while suppressing a link with any cognitive effort related to the thermometer bar (i.e., the slope a from the SN to the CEN and the slope b from the CEN to the DMN). Our results showed negative correlation between the cardiac cycles and either a or b and positive correlation between the cardiac cycles and the mindfulness scores. Previous studies seem to support our findings, in which an increase in cardiac cycles has been associated with increased sympathetic activity of the autonomic nervous system (ANS), which is related to the suppression of external stimuli (Lacey and Lacey, 2017; Laumann et al., 2003). However, a more systematic investigation is warranted to analyze our data in the context of ANS activity, such as by using heart rate variability, which is believed to better reflect the parasympathetic and sympathetic activity of the ANS (Amihai and Kozhevnikov, 2015; Holsen et al., 2011; Krygier et al., 2013; Tang et al., 2009).

Effective connectivity of the triple networks

The effective connectivity results obtained from our experimental data seem to provide supplemental evidence supporting our hypothesized model of mindfulness in the triple networks framework. For example, the results of the mediation analysis showed that, in the rtfMRI-NF runs, the regression coefficient (i.e., slope) from the SN to the DMN, as mediated by the CEN, presented greater levels of correlation with mindfulness scores and task-performance feedback scores than the slope from the DMN to the SN. Moreover, our effective connectivity analysis also suggested that mindfulness status that is reflected in the DMN (Brewer and Garrison, 2014; Mooneyham et al., 2016; Uddin, 2015) as well as the cognitive control in the CEN (Mooneyham et al., 2016; Seeley et al., 2007) also caused the activations related to the interoceptive perception of the SN (Farb et al., 2013) in the rtfMRI-NF runs. Interestingly, in the transfer run, the SN and CEN caused the activations in the DMN. It is possible that this effective connectivity change was associated with the presence and absence of the neurofeedback interface (i.e., thermometer bar) in the rtfMRI-NF and transfer runs, respectively. On the other hand, with the control group, there was no significant effective connectivity between interoceptive perception

(i.e., the SN) and mindfulness status (i.e., the DMN). This finding is consistent with other results on the absence of significant correlations between the regression coefficients (i.e., c') from the SN to the DMN and mindfulness/task-performance scores in the control group. In fact, the potentially positive correlation between inter-network effective connectivity from the CEN to the DMN and the task-performance feedback score in the transfer run of the control group is also consistent with the positive correlations of the control group between regression coefficient b in the mediation analysis and the task-performance feedback scores (Fig. 6b). The causal relationships between the triple networks can also be derived from the Granger causality analysis (Cohen Kadosh et al., 2016; Lee et al., 2012c).

Time spans of rtfMRI-NF training

A number of other studies have also reported a training effect guided by rtfMRI-NF within the relatively short training time of a single day (deCharms et al., 2005; Emmert et al., 2016; Haller et al., 2010; Kim et al., 2015a; Lee et al., 2012c; Lee et al., 2009; Marins et al., 2015; Perronnet et al., 2017; Yoo and Jolesz, 2002; Yoo et al., 2007; Yoo et al., 2008; Young et al., 2014; Zotev et al., 2011; Zotev et al., 2014). For example, in one of the seminal papers on rtfMRI-NF by deCharms et al. (2005), each run consisted of five blocks (1 minute/block) for each of the up-regulation and down-regulation phases of activation in the rostral anterior cingulate cortex (rACC) area, which has been related to chronic pain perception (deCharms et al., 2005) and an increase in the rACC BOLD signals was observed in the second rtfMRI-NF training run. In a series of studies employing rtfMRI-NF training for the amygdala activation by happy memory retrieval (Young et al., 2014; Zotev et al., 2011; Zotev et al., 2014), there were three runs of rtfMRI-NF training each featuring four blocks of happy memory retrieval training (40 s/block; 2 minutes 40 s/run; 8 minutes across the three runs) and an increase in the amygdala activation across these three rtfMRI-NF training runs was reported. In the study by Haller et al. (2010), in each of four rtfMRI-NF training runs, there was a period of about 2 minutes for participants having chronic tinnitus to learn the down-regulation of auditory activations, with the rtfMRI-NF training period totaling approximately 8 minutes. Using motor imagery as a target task strategy, increased activations in the motor areas have been reported after approximately 10 minutes of rtfMRI-NF training (Marins et al., 2015; Perronnet et al., 2017). In the meta-analysis of Emmert et al. (2016), several other studies

were reported to have used an overall rtfMRI-NF training length of less than approximately 10 minutes (for example, Berman et al. (2013), Sulzer et al. (2013), and Veit et al. (2012) (Berman et al., 2013; Emmert et al., 2016; Sulzer et al., 2013b; Veit et al., 2012)).

There have also been other rtfMRI-NF studies that were conducted across several days of training sessions (Scharnowski et al., 2015; Sherwood et al., 2016). For example, Scharnowski et al. (2015) reported that participants learned to up- and down-regulate the BOLD signal defined as the difference between the BOLD signals in the supplementary motor area and parahippocampal place area, by controlling motor- and memory-related activation (Scharnowski et al., 2015). In this study, participants took about 12-22 runs (i.e., three 45 s up-regulation blocks and three 45 s down-regulation blocks in one run) across 4-6 days to learn a significant level of self-regulation. Also, Sherwood et al. (2016) reported that participants took five rtfMRI-NF sessions across two weeks (16 minutes total; each session consisted of one run; four 48 s blocks/run, or 3 minutes 12 s/run) to learn to up regulate working memory performance based on the BOLD signal in the dorsolateral prefrontal cortex (Sherwood et al., 2016).

It is also important to note that rtfMRI-NF training methods using indirect and/or covert information transformed from brain data as a neurofeedback signals tend to adopt a prolonged training period (Ramot et al., 2016; Shibata et al., 2011). For example, Ramot et al. (2016) reported that each participant performed five consecutive rtfMRI-NF runs (10 minutes/run) per day across 5 separate days to learn to regulate the differential activation of two category-selective visual perception areas (i.e., fusiform area and parahippocampal place area) via covert neurofeedback information (i.e., reward) (Ramot et al., 2016). In the study by Shibata et al. (2011), rtfMRI-NF training to learn the induction of activation patterns in the early visual cortex was conducted during 5 or 10 days using the information from a pre-trained fMRI decoder. Across subjects and days, an average of 10.8 runs of rtfMRI-NF training (5 minutes/run) was conducted in each day (Shibata et al., 2011). It would be an interesting meta-analysis study to systematically investigate the time span of rtfMRI-NF training depending on

whether the neurofeedback information was comprised of direct/overt information (i.e., brain activation and connectivity) or indirect/covert information (e.g., reward and/or decoded information).

Strength of the study, potential weakness, and future works

One major strength of our study was that we evaluated potential functional features of mindfulness using independently measured mindfulness scores by systematically changing the mediation analysis models of the triple networks. In addition, our results from Pearson's correlation and partial correlation analyses were compared with the results from the mediation analysis to further justify the partial regression coefficient (i.e., slope) level from the SN to the DMN, as mediated by the CEN, being one of the functional features of mindfulness in our experimental setting.

Precautions were taken to ensure that the experimenters and participants were blind to the group assignment. Notwithstanding, the experimenter who developed our rtfMRI-NF software toolbox and executed the software during the MRI session (i.e., first author of this paper) was aware of the group assignment of the participants so that he could properly operate the software toolbox on MRI session day since the neurofeedback information of the participants in the control group had to be substituted with the neurofeedback information of their paired participants in the experimental group. However, it is important to note that this experimenter, who also performed the data analyses, did not collect any of the subjective ratings in the pre- and post-MRI sessions. Instead, other staff members (S.J., J.L., and D.-Y. K. of co-authors) who were blinded to the assignment interviewed and collected the questionnaires from the participants. Also, the SMS_S and TPF scores obtained from the rtfMRI-NF training runs and transfer runs (Fig. 1b) were automatically recorded via our software toolbox without any interaction with the participants.

The initial ROIs of the triple networks were fine-tuned in individual native EPI space by applying ICA to two concatenated three-minute resting-state blocks (Beckmann and Smith, 2004) based on an independence assumption across spatial patterns (i.e., spatial ICA) (McKeown et al., 1998a). The spatial patterns from the spatial ICA have had their reproducibility and/or reliability demonstrated

across different sessions/runs and different tasks (Calhoun et al., 2008; Damoiseaux et al., 2006; De Luca et al., 2006; Mennes et al., 2010; Van Den Heuvel and Pol, 2010; Zuo et al., 2010). For example, Calhoun et al., (2008) reported that the spatial patterns obtained from the spatial ICA were preserved overall across an auditory oddball task and resting-state periods (Calhoun et al., 2008). Thus, we believe that our extracted spatial patterns of the triple networks taken during the resting-state blocks would not be subject to a critical confounding effect from the preceding tasks (i.e., mindfulness, mind-wandering, and/or three cognitive tasks). Nonetheless, it is worth noting the possibility of a potential residual/confounding effect from the preceding tasks affecting the resting-state blocks, particularly in the time courses of the spatial patterns (Albert et al., 2009; Gordon et al., 2014; Tung et al., 2013).

Considering the distinct functions of the subdivisions of the insula (Uddin, 2015), the ROI of the SN may need to be fine-tuned further to include only its right dorsal anterior insular cortex, known as the 'causal hub' of the SN, which influences other large-scale brain networks, including the CEN and DMN (Sridharan et al., 2008). In addition, further study is warranted to determine whether our rtfMRI-NF-based mindfulness training also alters FC changes between the subnetworks of the DMN (Mooneyham et al., 2016). In order to deploy mindfulness training via EEG based neurofeedback, an important future work would be to investigate the EEG features of mindfulness, such as the rhythmic activities of our EEG data, which was simultaneously acquired with fMRI (Kim et al., 2015b; Tsuchimoto et al., 2017).

In addition, it is possible that the neuronal circuitry of mindfulness may involve brain networks other than the triple networks which were scrutinized in our study. To accommodate such scenarios, the development of a model that can handle more than three networks is necessary. For example, machine learning approaches, including deep neural networks, may be gainfully utilized to extract the representative functional features of mindfulness from the FC levels obtained from all possible combinatorial pairs of brain networks, such as in the automated anatomical labeling atlas (Jang et al., 2017; Kim et al., 2016). In this context, applying machine learning approaches to our non-rtfMRI data

acquired during mindfulness and mind-wandering, such as to classify the task type and/or to predict the behavioral score (Kim et al., 2018) is an important future work.

It is unlikely that the sequence-of-condition during ambulatory training (i.e., mindfulness on the first day and mind-wandering on the second day and so on, MF ⇄ MW, or vice versa, MW ⇄ MF) affects the results of the rtfMRI-NF effect reported in our study. This is because there was no main effect of the sequence-of-condition in (a) the PSS, MDMQ, SMS, VAS, and TPF scores obtained on the last day of ambulatory training and (b) the MDMQ, SMS, and VAS scores obtained in the pre-MRI session. The interaction between the group and the sequence-of-condition using the TPF scores is interesting (Fig. S1c). However, these results using the stratified sub-group based on the sequence-of-condition during ambulatory training need careful interpreted since (i) there were an unequal number of subjects (Table 2) which might potentially lead to a biased result and (ii) there was a limited number of participants (n = 10; sometimes 9 due to an outlier participant amongst the scores) for the MW ⇄ MF condition in the control group. It is interesting that there seems to be an effect from ambulatory training over time, particularly on the MDMQ calm-nervous scores and mindfulness scores. Future study is warranted to systematically investigate whether the smartphone-based ambulatory training conducted as a part of our study was efficient as an intervention tool to improve mood (Meinlschmidt et al., 2016) and whether prolonged longitudinal ambulatory training consolidates the potential learning effect (Garrison et al., 2015; Mason et al., 2018; Noone and Hogan, 2018).

Mediation analysis using the triple networks appears to be well suited to our rtfMRI-NF experimental setup, in which the SN is associated with multisensory interoception (i.e., focused attention to the physical sensations of breathing), the DMN is related to the endogenous event (i.e., the self-referential perception of mindfulness), and the CEN is linked to the exogenous event (i.e., the changing thermometer bar). Although this triple network model of mindfulness appeared to be less-fitted to our data collected during the transfer run when there was no thermometer bar (i.e., Fig. 5b), the effective connectivity analysis suggested that the CEN had the causal effect to the DMN in the transfer run (i.e., Fig. 12b). This indicates that the CEN may also be involved when the mindfulness

strategy is employed without a thermometer bar, possibly to reduce distracting thoughts involving cognitive processes (i.e., mind-wandering) that would otherwise interfere with the self-referential perception of mindfulness. Thus, whether our mediation analysis model using the triple networks is also well suited to naturalistic scenarios of mindfulness meditation outside of MRI and without neurofeedback information is an interesting question. In this context, a longitudinal study to acquire fMRI data from mindfulness-meditation-naïve subjects across multiple time-points during the course of mindfulness training in a naturalistic condition (i.e., outside of an MRI) is warranted. This type of study would serve to evaluate whether prolonged mindfulness training leads to an enhancement of mindfulness status and whether this enhancement is reflected in the functional features of mindfulness.

In our study, attention focused on the physical sensations of breathing was adopted as a mindfulness strategy, and mindfulness-meditation-naïve individuals participated in this cross-sectional study. However, a variety of alternative mindfulness practices exist, including open-monitoring practices, as well as various methodological designs such as a longitudinal study (Rance et al., 2018) and/or comparing results between expert meditators and either non-meditator controls, beginning meditators, or less experienced meditators (Mooneyham et al., 2016). An important research question to answer is whether our presented method and the proposed partial regression coefficient feature of mindfulness can provide converging evidence on the mindful brain across all these diverse mindfulness scenarios.

Conclusions

In this study, we presented a potential functional feature of mindfulness (i.e., the partial regression coefficient from the SN to the DMN, as mediated by the CEN, modeled by mediation analysis of the triple networks) from mindfulness-meditation-naïve participants. In addition, we demonstrated the possibility of enhancing this functional feature via rtfMRI-NF-based mindfulness training. The validity of this functional feature of mindfulness was systematically evaluated using independently measured subjective ratings of mindfulness scores, and by comparing alternative FC levels in the triple networks obtained by Pearson's correlation and partial correlation analyses. Since the triple networks can model

aberrant saliency mapping and cognitive dysfunction across a span of mental and neurological disorders (Menon, 2011), as well as the typical development of the human brain (Uddin et al., 2011) and emotion (Touroutoglou et al., 2015; Young et al., 2017), the presented mediation analysis model across the triple networks may be a viable tool widely applicable to the treatment of mental and neurological disorders using rtfMRI-NF training.

Appendix

Appendix A. Functional connectivity (FC) level from the Pearson's correlation analysis

The Pearson's correlation coefficient can be used to estimate the level of FC between the SN and the DMN as follows (Cohen et al., 2013):

$$c = \frac{\frac{1}{n}\sum_{t=1}^{n}[(x(t)-\mu_x)(y(t)-\mu_y)]}{\sqrt{\frac{1}{n}\sum_{t=1}^{n}(x(t)-\mu_x)^2}\sqrt{\frac{1}{n}\sum_{t=1}^{n}(y(t)-\mu_y)^2}} = \frac{\sigma_{xy}}{\sigma_x\sigma_y} = r_{xy} \quad \text{(A. 1)}$$

where $x(t)$ is the BOLD signal of the SN at time t, $y(t)$ is the BOLD signal of the DMN, n is the number of time points (i.e., TRs) in the BOLD signal, r_{xy} is the Pearson's correlation coefficient between $x(t)$ and $y(t)$, μ_x and μ_y are the mean values of $x(t)$ and $y(t)$, respectively, σ_{xy} is the covariance between the two variables, and σ_x and σ_y are the standard deviations of $x(t)$ and $y(t)$, respectively.

Appendix B. Regression coefficients (i.e., slopes) from the mediation analysis

In the mediation analysis model of the triple networks (Fig. 2a), the BOLD signal of the DMN, $y(t)$ (i.e., denoted as column vector $\boldsymbol{y}$; dependent variable) can be represented as a linear summation of the BOLD signal of the SN, $x(t)$ (i.e., denoted as column vector $\boldsymbol{x}$; independent variable) and the BOLD signal of the CEN, $m(t)$ (i.e., denoted as column vector $\boldsymbol{m}$; mediator variable) (MacKinnon et al., 2007):

$$\boldsymbol{y} = c'\boldsymbol{x} + b\boldsymbol{m} + b_1 + \boldsymbol{e_1} \quad \text{(A.2)}$$

where $c'$and b are the regression coefficients (i.e., slopes) for predicting $\boldsymbol{y}$ using the predictors $\boldsymbol{x}$ and $\boldsymbol{m}$, respectively, b_1 is a bias term to adjust for the baseline BOLD intensity of $\boldsymbol{y}$, and $\boldsymbol{e_1}$ is the residual. Similarly, the mediator variable $\boldsymbol{m}$ can be represented using the independent variable $\boldsymbol{x}$:

$$\boldsymbol{m} = a\,\boldsymbol{x} + b_2 + \boldsymbol{e_2} \quad \text{(A.3)}$$

where a is the regression coefficient of the predictor $\boldsymbol{x}$, b_2 is a bias term, and $\boldsymbol{e_2}$ is the residual.

From Eqs. (A.2) and (A.3),

$$\boldsymbol{y} = c'\boldsymbol{x} + b(a\,\boldsymbol{x} + b_2 + \boldsymbol{e_2}) + b_1 + \boldsymbol{e_1} = (c' + ab)\boldsymbol{x} + bb_2 + b_1 + b\boldsymbol{e_2} + \boldsymbol{e_1} = c\boldsymbol{x} + b_3 + \boldsymbol{e_3} \quad \text{(A.4)}$$

where c $(= c' + ab)$ is the regression coefficient (i.e., total effect) from the predictor $\boldsymbol{x}$ to the response variable $\boldsymbol{y}$, b_3 is a bias term, and $\boldsymbol{e_3}$ is the residual.

Eq. (A.2) is equivalent to the following equation:

$$\boldsymbol{y_0} = [\boldsymbol{x_0} \quad \boldsymbol{m_0}] \begin{bmatrix} c' \\ b \end{bmatrix} + \tilde{\boldsymbol{e}}_{\boldsymbol{1}} \tag{A.5}$$

where $\boldsymbol{y_0}$, $\boldsymbol{x_0}$, and $\boldsymbol{m_0}$ are the zero-meaned $\boldsymbol{y}$, $\boldsymbol{x}$, and $\boldsymbol{m}$, respectively, and $\tilde{\boldsymbol{e}}_1$ is the residual from the zero-meaned variables. Applying the least-squares (LS) algorithm to Eq. (A.5):

$$\begin{bmatrix} c' \\ b \end{bmatrix} = ([\boldsymbol{x}_0 \quad \boldsymbol{m}_0]^T [\boldsymbol{x}_0 \quad \boldsymbol{m}_0])^{-1} [\boldsymbol{x}_0 \quad \boldsymbol{m}_0]^T \boldsymbol{y_0} = \begin{bmatrix} \boldsymbol{x_0}^T \boldsymbol{x_0} & \boldsymbol{x_0}^T \boldsymbol{m_0} \\ \boldsymbol{m_0}^T \boldsymbol{x_0} & \boldsymbol{m_0}^T \boldsymbol{m_0} \end{bmatrix}^{-1} \begin{bmatrix} \boldsymbol{x_0}^T \boldsymbol{y_0} \\ \boldsymbol{m_0}^T \boldsymbol{y_0} \end{bmatrix} \tag{A.6}$$

Now, $\boldsymbol{x_0}^T \boldsymbol{x_0} = \sigma_x^2$, $\boldsymbol{m_0}^T \boldsymbol{m_0} = \sigma_m^2$, $\boldsymbol{x_0}^T \boldsymbol{m_0} = \boldsymbol{m_0}^T \boldsymbol{x_0} = r_{xm}\sigma_x\sigma_m$, $\boldsymbol{x_0}^T \boldsymbol{y_0} = r_{xy}\sigma_x\sigma_y$, $\boldsymbol{m_0}^T \boldsymbol{y_0} = r_{my}\sigma_m\sigma_y$, where σ_i is the standard deviation of the variable i and r_{ij} is the Pearson's correlation coefficient between variables i and j. Thus, the LS solution in Eq. (A.6) becomes:

$$c' = \frac{r_{xy} - r_{xm}r_{my}}{1 - r_{xm}^2} \frac{\sigma_y}{\sigma_x}, \qquad b = \frac{r_{my} - r_{xy}r_{xm}}{1 - r_{xm}^2} \frac{\sigma_y}{\sigma_m} \tag{A.7}$$

Similarly, from the LS solution of Eq. (A.3):

$$a = r_{xm} \frac{\sigma_m}{\sigma_x} \tag{A.8}$$

Appendix C. Comparison between the mediation analysis and partial correlation analysis

The partial correlation coefficient can be used to estimate the level of FC between the SN and DMN with an adjusting variable from the CEN as follows (Cohen et al., 2013):

$$r_{xy \cdot m} = \frac{r_{xy} - r_{xm}r_{my}}{\sqrt{(1 - r_{xm}^2)(1 - r_{my}^2)}} \tag{A. 9}$$

Now, let's suppose the two scenarios of no mediation effect (i.e., ab = 0, when a=0 or b=0):

(i) When a = 0 (i.e., $r_{xm} = 0$):

$$c' = r_{xy} \frac{\sigma_y}{\sigma_x} \qquad (= c;\ \therefore \text{ same as the total effect}) \tag{A. 10}$$

$$r_{xy \cdot m} = \frac{r_{xy}}{\sqrt{(1 - r_{my}^2)}} \ (\geq r_{xy};\ \therefore \text{ greater than or equal to the simple correlation}) \tag{A. 11}$$

(ii) When b = 0 (i.e., $r_{my} = r_{xy}r_{xm}$):

$$c' = \frac{r_{xy} - r_{xm}r_{my}}{1 - r_{xm}^2} \frac{\sigma_y}{\sigma_x} = r_{xy} \frac{\sigma_y}{\sigma_x} \qquad (= c;\ \therefore \text{ same as the total effect}) \tag{A.12}$$

$$r_{xy\cdot m} = \frac{r_{xy} - r_{xm}r_{my}}{\sqrt{(1 - r_{xm}^2)(1 - r_{my}^2)}} = r_{xy}\frac{\sqrt{(1 - r_{xm}^2)}}{\sqrt{(1 - r_{xy}^2\, r_{xm}^2)}} (\leq r_{xy};\ \therefore \text{ smaller than or equal to the simple correlation}) \quad \text{(A.13)}$$

In summary, when there is no mediation effect, the direct effect (i.e., c') is the same as the total effect (i.e., c) whereas the partial correlation coefficient (i.e., $r_{xy\cdot m}$) is not always the same as the simple correlation coefficient (i.e., r_{xy}). Therefore, the partial correlation coefficient cannot inform the mediation effect.

Now, let's suppose that the simple correlation between the independent variable and mediator variable (i.e., r_{xm}) is the same as the simple correlation between the mediator variable and dependent variable (i.e., r_{my}), i.e., $r_{xm} = r_{my}$. From Eqs. (A.7) and (A.9),

$$c' = \frac{r_{xy} - r_{xm}^2}{1 - r_{xm}^2}\frac{\sigma_y}{\sigma_x} = r_{xy\cdot m}\frac{\sigma_y}{\sigma_x} \quad \text{(A.14)}$$

Thus, the direct effect between the independent variable and dependent variable is the same as the partial correlation coefficient when these variables are standardized.

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Figure Legends

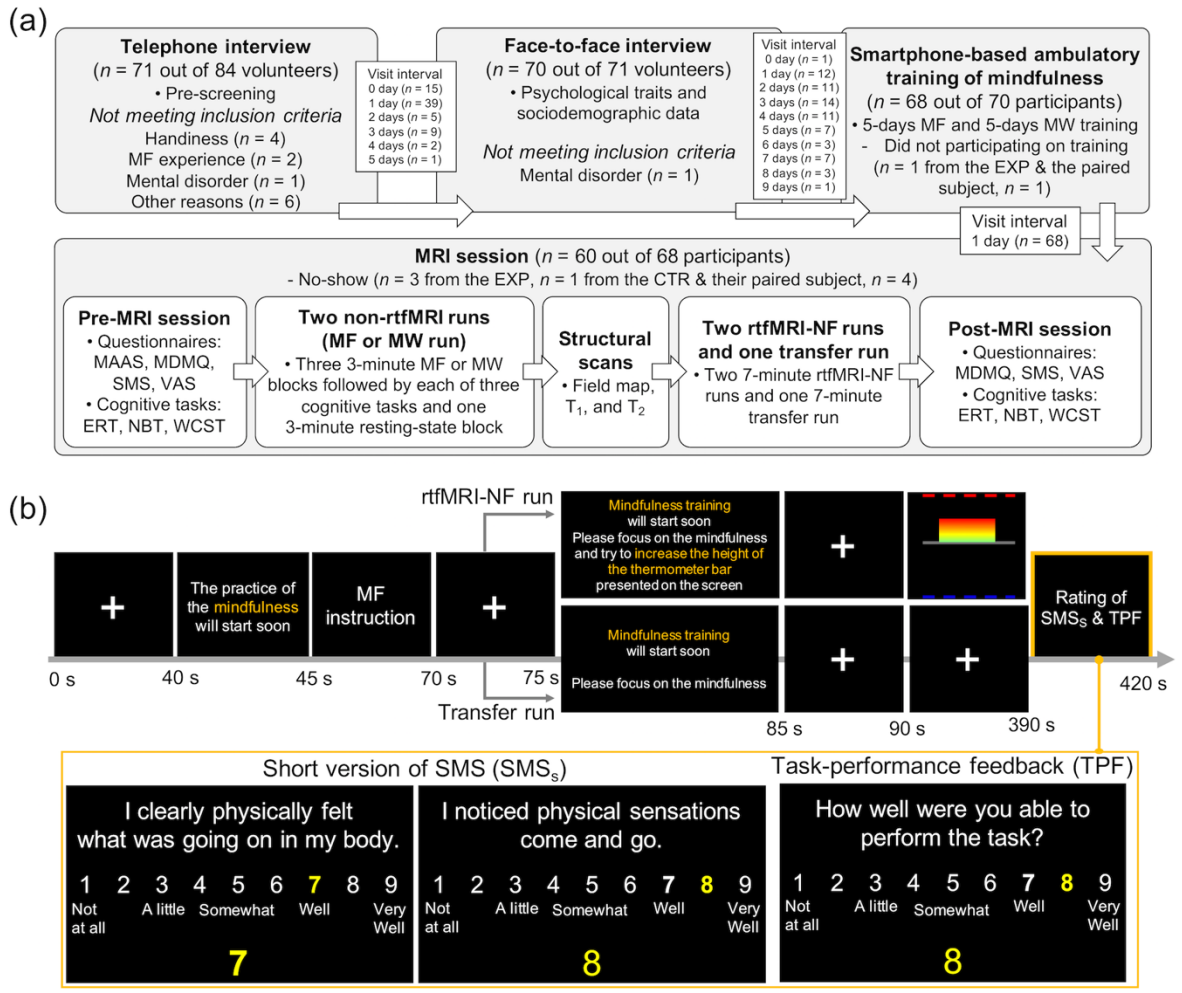

Figure 1. (a) The overall study protocol including time intervals between sessions and number of participants included/excluded from the screened participants. (b) Task paradigm for the rtfMRI-NF run and the transfer run. See the "***Overall study protocol***" and "***Two real-time fMRI neurofeedback runs and one transfer run: online analysis***" subsection in the Methods section for details. The mindfulness instruction is described in Table 1. ERT, Emotion Recognition Task; MAAS, Mindful Attention Awareness Scale; MDMQ, Multidimensional Mood State Questionnaire; MF, mindfulness; MW, mind-wandering; NBT, *n*-back task (i.e., 3-back); non-rtfMRI, non-real-time fMRI; SMS, State Mindfulness Scale; VAS, Visual Analog scale for Stress perception; WCST, Wisconsin Card Sorting Test.

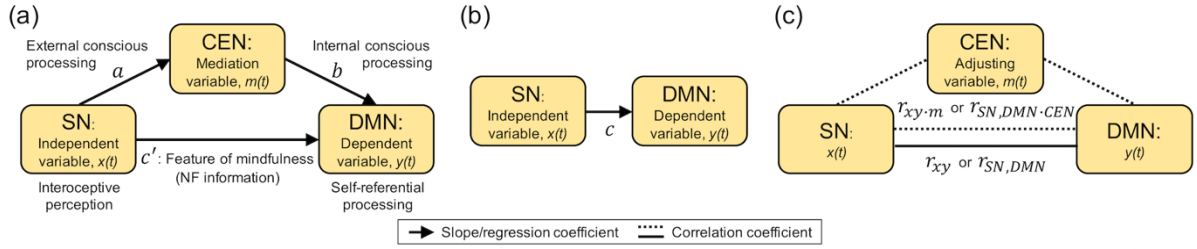

Figure 2. (a) The proposed mediation analysis model of the triple networks for mindfulness training by rtfMRI-NF and transfer runs (see "***Appendix B. Regression coefficients (i.e., slopes) from the mediation analysis***" for details). (b) The un-mediated model between the SN and DMN. (c) Simple correlation (r_{xy}, a solid line) and partial correlation ($r_{xy\cdot m}$, dashed lines) models in the triple networks. CEN, central executive network; DMN, default-mode network; NF, neurofeedback; ROI, region-of-interest; SN, salience network.

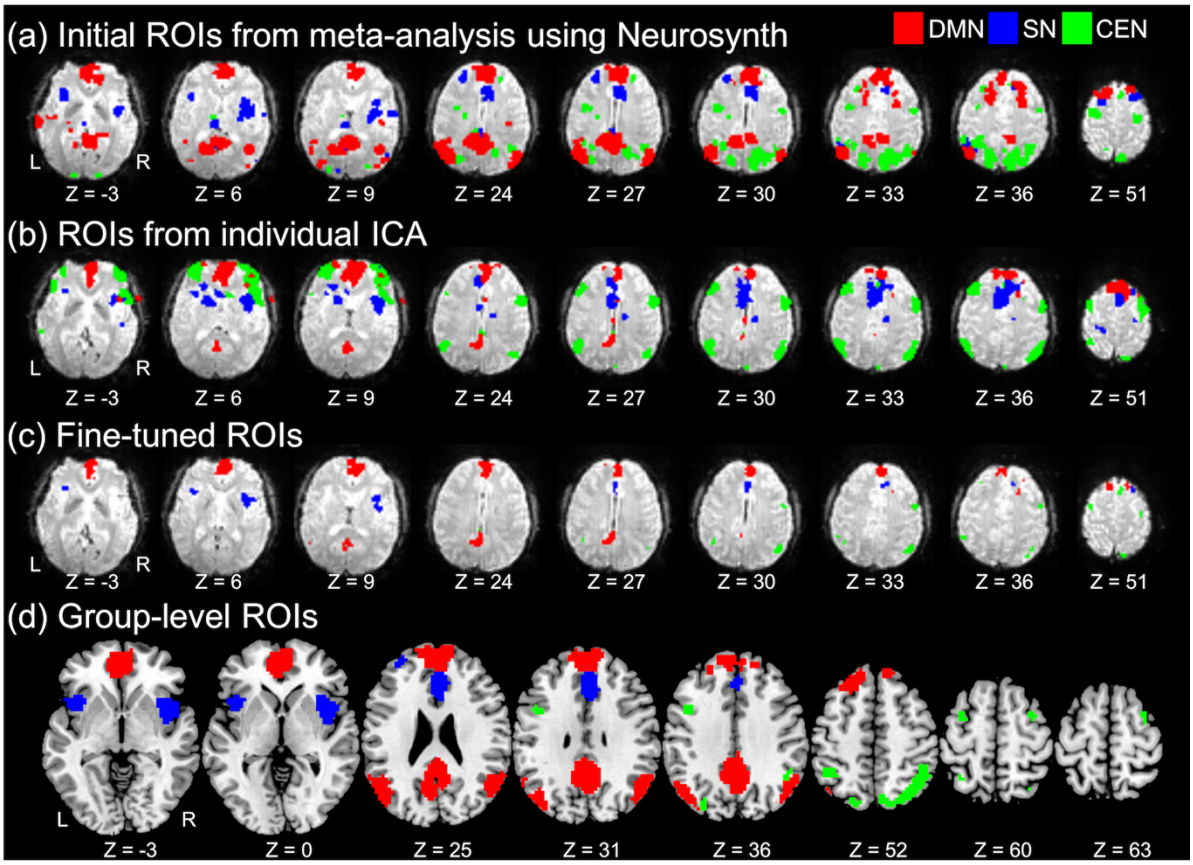

Figure 3. ROIs of the triple networks. (a) ROIs were initialized from term-based meta-analysis using the Neurosynth repository (neurosynth.org) and projected onto the individual EPI space (false discovery rate or FDR $p < 0.01$). (b) ROIs obtained from the spatial independent component analysis (ICA) using the individual resting-state fMRI data from two non-rtfMRI runs (z-score > 1.96 or uncorrected $p < 0.05$). (c) The fine-tuned ROIs employed in the rtfMRI-runs obtained from the intersection of (a) and (b). (d) Group-level fine-tuned ROIs obtained from the one-sample *t*-test across all participants (FDR < 0.01, with a minimum of 10 connected voxels). See the "***Regions-of-interest definition of the triple networks***" subsection in the Methods section and "***Fine-tuning of regions-of-interest of the triple networks using individual fMRI data***" subsection in the Supplementary Materials for details. L, left; R, right; CEN, central executive network; DMN, default-mode network; rtfMRI, real-time fMRI; SN, salience network.

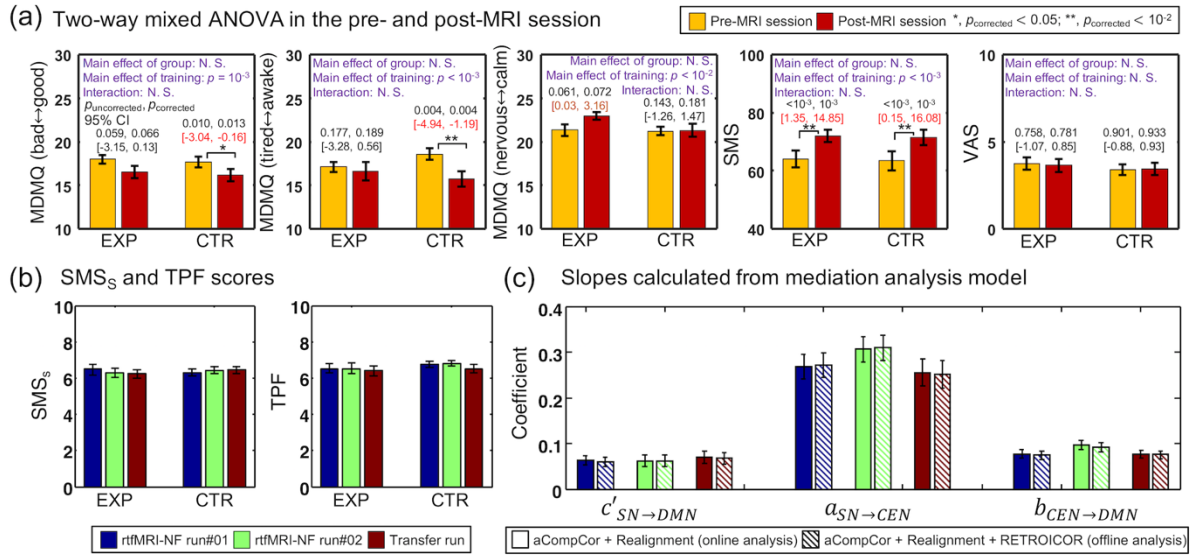

Figure 4. Behavioral data (a-b) and regression coefficient (i.e., slope) levels from the online and offline analyses (c). (a) Behavioral data obtained from Multidimensional Mood State Questionnaire (MDMQ), State Mindfulness Scale (SMS), and Visual Analog scale for Stress perception (VAS), scores obtained before (pre-MRI) and after (post-MRI) the MRI session. A two-way (i.e., 2 [groups; EXP or CTR] × 2 [training types; pre- or post-MRI session]) mixed analysis-of-variance was applied. The confidence intervals (CIs) in red and orange are identified as "significant" and "weakly suggestive", respectively. (b) Scores from the short version of the SMS (or SMS_S) and task-performance feedback (TPF) obtained in the two rtfMRI-NF runs and one transfer run. (c) Slope levels calculated from the mediation analysis model using the triple networks in the online analysis (i.e., nuisance regression with three translational and three rotational head motion parameters, and physiological noise correction using aCompCor) and the offline analysis (i.e., the same nuisance regression and physiological noise correction using aCompCor and, additionally, RETROICOR). See the "***Overall study protocol***" subsection in the Methods section and "***Data from subjective ratings and raw fMRI***" subsection in the Results section for details. The vertical bars and whiskers represent the mean and standard error, respectively. The a, b, and c' are the slope levels between the corresponding pairs in the triple networks (Fig. 2). aCompCor, a component based noise correction method; CEN, central executive network; CTR, control group; DMN, default-mode network; EXP, experimental group; rtfMRI-NF, real-time fMRI neurofeedback; RETROICOR, RETROspective Image CORrection; SN, salience network.

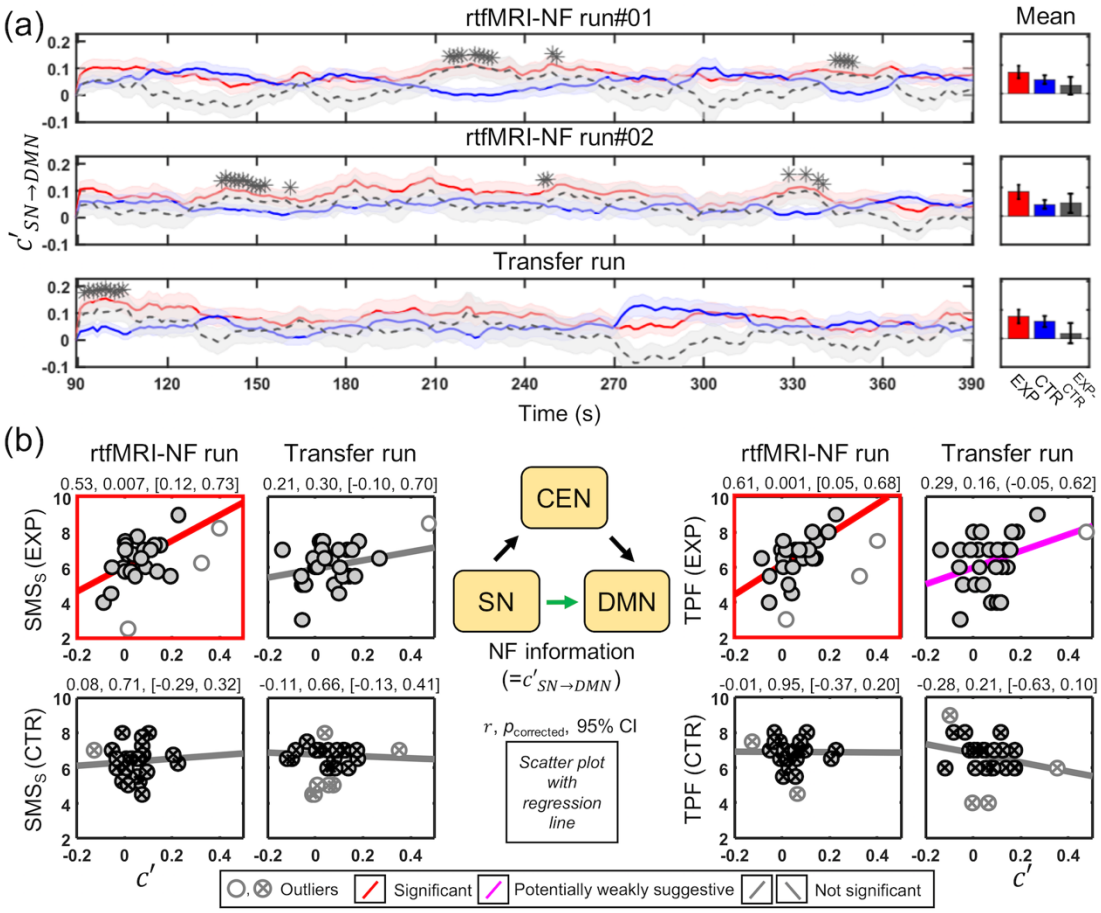

Figure 5. The partial regression coefficient (i.e., slope) levels from the SN to the DMN mediated by the CEN (i.e., c') and their association with the SMS_S (i.e., mindfulness scores) and TPF scores. (a) Time plots of the c' value along the two rtfMRI-NF runs and one transfer run (line: mean across all subjects; shaded areas: standard errors of the mean). Any time-point where the paired differences (dark gray) of slope values between the experimental (red) and control (blue) groups were significantly non-zero (corrected $p < 0.05$ excluding outliers) was denoted by an asterisk *. (b) Scatter plots using the neurofeedback information (i.e., c') in the mediation analysis and SMS_S or TPF scores for each of the two groups (top row: experimental group; bottom row: control group). CEN, central executive network; CTR, control group; DMN, default-mode network; EXP, experimental group; rtfMRI-NF, real-time fMRI neurofeedback; SMS_S, short version of the State Mindfulness Score; SN, salience network; TPF, task-performance feedback. Detailed information about outliers, *p*-value correction of correlation coefficient (i.e., *r*), confidence interval (CI), and stratified scenarios of statistical significance is presented in Table 3.

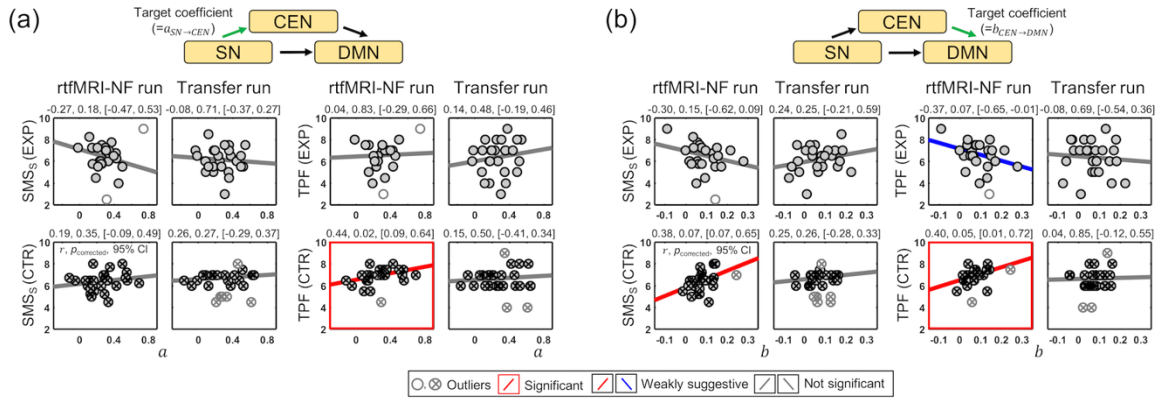

Figure 6. Scatter plots of (a) the regression coefficient (i.e., slope) levels from the SN to the CEN (i.e., a) and the SMS$_S$/TPF scores and (b) the slope levels from the CEN to the DMN (i.e., b) and the SMS$_S$/TPF scores. CEN, central executive network; CTR, control group; DMN, default-mode network; EXP, experimental group; rtfMRI-NF, real-time fMRI neurofeedback; SMS$_S$, short version of the State Mindfulness Scale; SN, salience network; TPF, task-performance feedback. Detailed information about outliers, p-value correction of correlation coefficient (i.e., r), confidence interval (CI), and stratified scenarios of statistical significance is presented in Table 3.

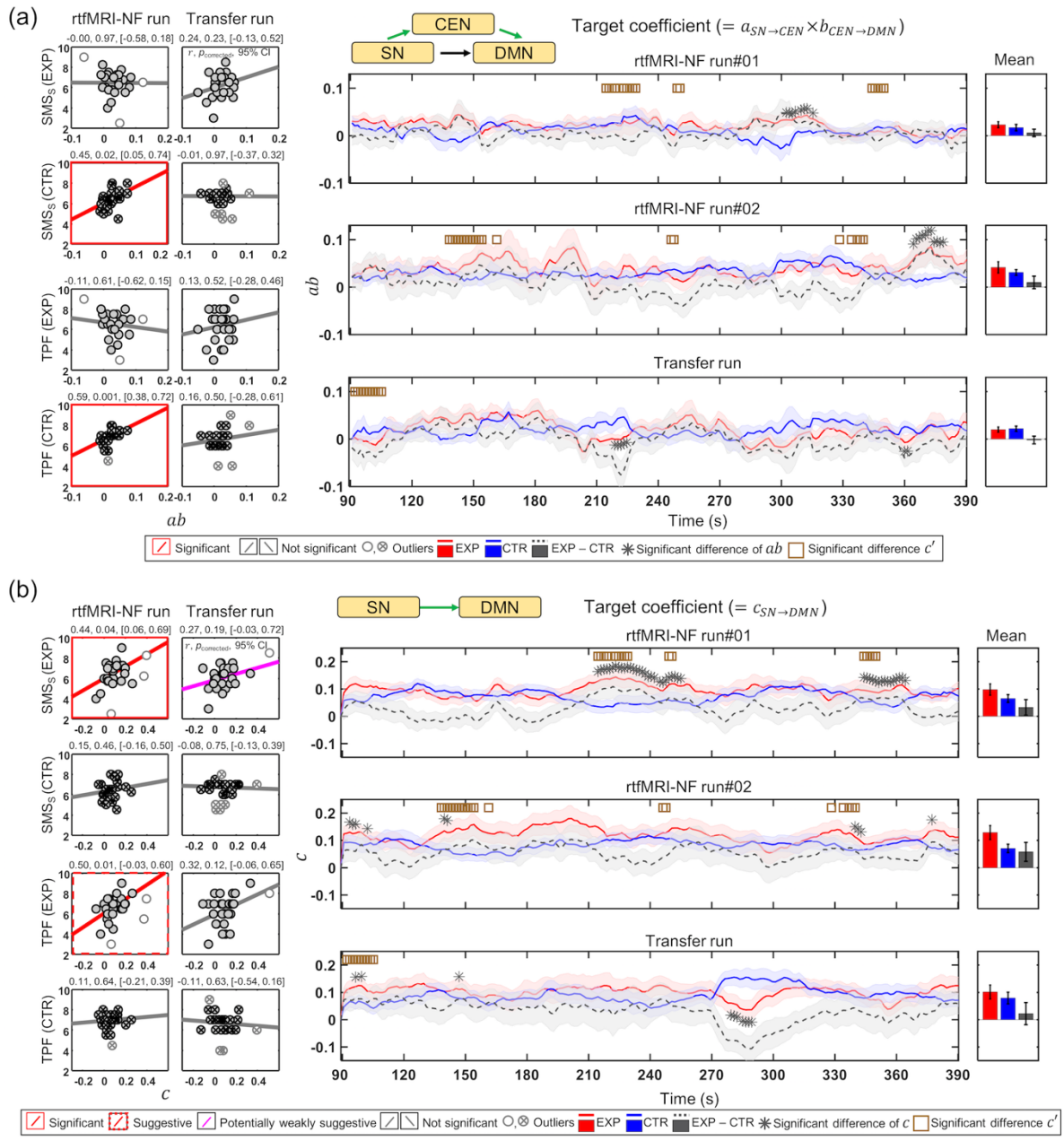

Figure 7. Scatter plots of (a) the regression coefficient (i.e., slope) values of ab and SMS$_S$/TPF scores and (b) the slope value of c and the SMS$_S$/TPF scores and their time plots (line: mean across all subjects; shaded areas: standard errors of the mean) across the two rtfMRI-NF runs and one transfer run along with the mean and standard error across the time points. CTR, control group; DMN, default-mode network; EXP, experimental group; rtfMRI-NF, real-time fMRI neurofeedback; SMS$_S$, short version of the State Mindfulness Scale; SN, salience network; TPF, task-performance feedback. Detailed information about outliers, *p*-value correction of correlation coefficient (i.e., *r*), confidence interval (CI), and stratified scenarios of statistical significance is presented in Table 3.

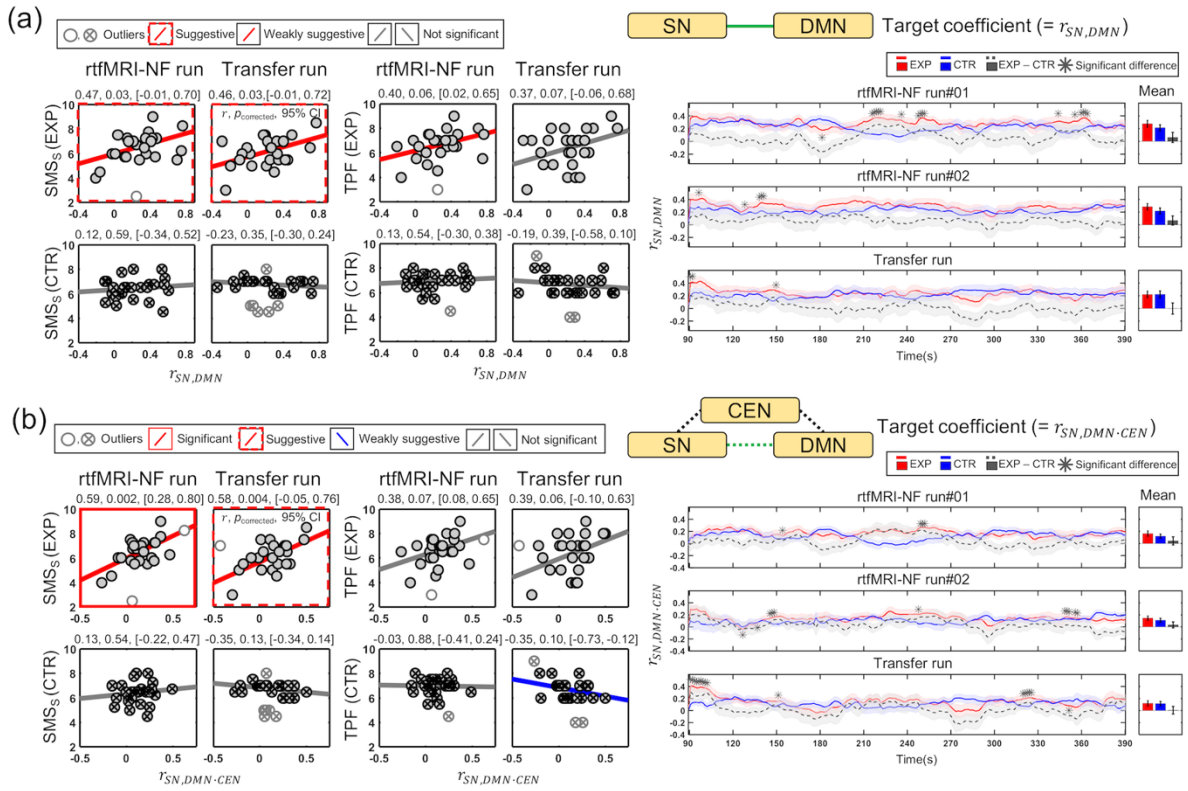

Figure 8. Scatter plots using the functional connectivity (FC) levels between either (a) the SN and DMN from the Pearson's correlation analysis or (b) the SN and DMN with the adjusting variable from the CEN from the partial correlation analysis, and either the SMS_S or TPF scores. The line plots of the FC levels for each of the two rtfMRI-NF runs and one transfer run (line: mean across all subjects; shaded areas: standard errors of the mean). CEN, central executive network; DMN, default-mode network; SN, salience network; SMS_S, short version of the State Mindfulness Score; TPF, task-performance feedback; rtfMRI-NF, real-time fMRI neurofeedback; EXP, experimental group; CTR, control group. Detailed information about outliers, *p*-value correction of correlation coefficient (i.e., *r*), confidence interval (CI), and stratified scenarios of statistical significance is presented in Table 3.

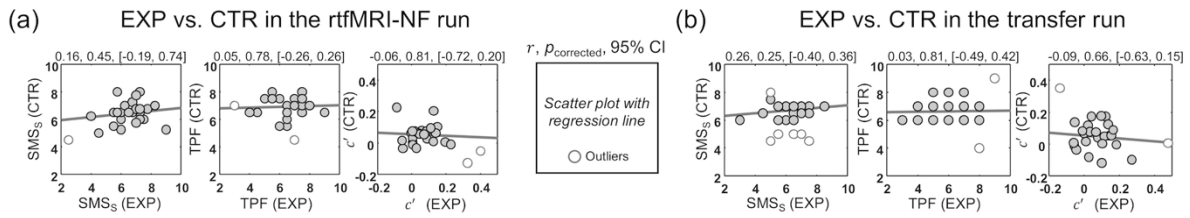

Figure 9. Scatter plots of the c' values, SMS_S scores and TPF scores from the paired participants across the two groups in (a) the rtfMRI-NF run and (b) transfer run. CTR, control group; EXP, experimental group; rtfMRI-NF, real-time fMRI neurofeedback; SMS_S, short version of the State Mindfulness Scale. TPF, task-performance feedback. Detailed information about outliers, *p*-value correction of correlation coefficient (i.e., *r*), and confidence interval (CI) is presented in Table 3.

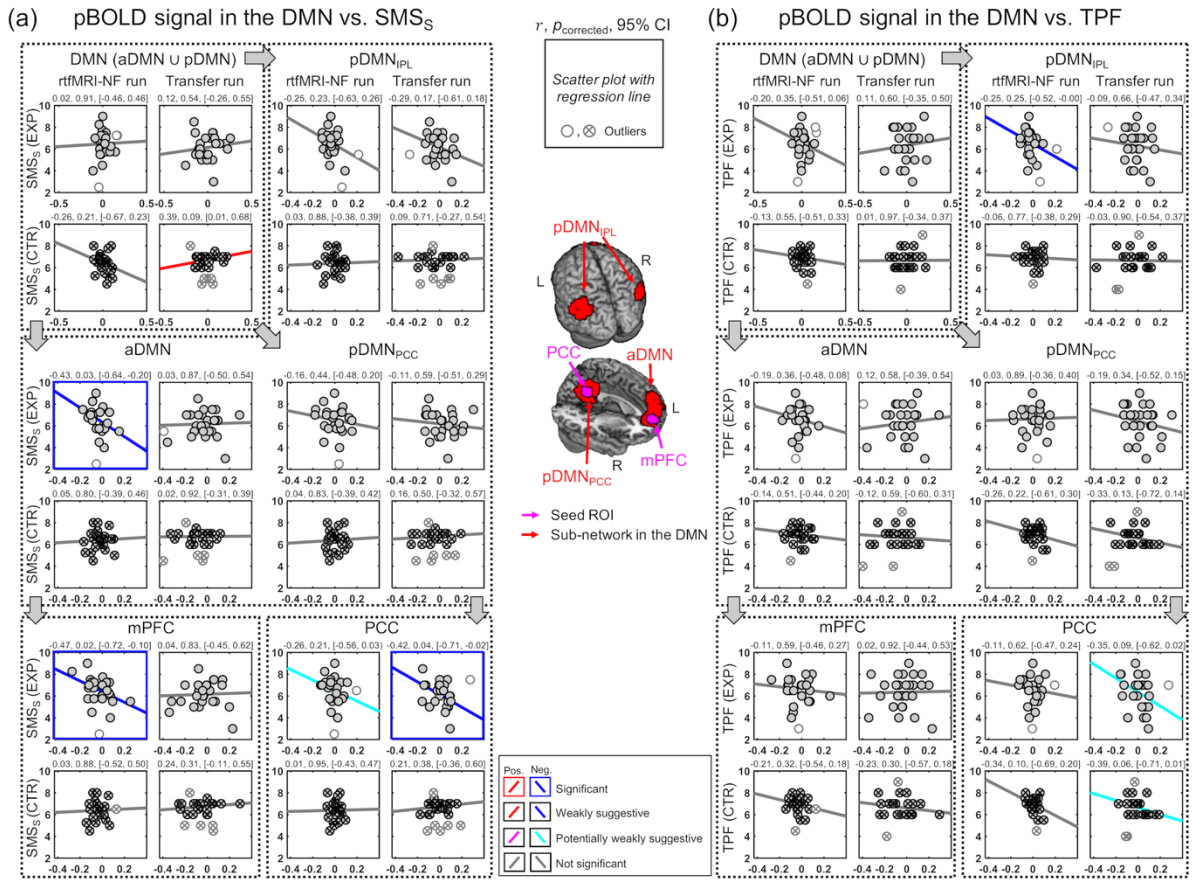

Figure 10. Scatter plots of the percentage blood-oxygenation-level-dependent (pBOLD) signal obtained from each ROI within the default-mode network (DMN) and the SMS_S (a) or TPF (b) scores in the rtfMRI-NF runs and transfer run. L, left; R, right; aDMN, anterior DMN; CTR, control group; EXP, experimental group; IPL, inferior parietal lobule; Neg., Negative; N.S., non-significant; mPFC, medial prefrontal cortex; PCC, posterior cingulate cortex; pDMN, posterior DMN; Pos., Positive; ROI, region-of-interest; rtfMRI-NF, real-time fMRI neurofeedback; SMS_S, short version of the State Mindfulness Scale; TPF, task-performance feedback. Detailed information about outliers, *p*-value correction of correlation coefficient (i.e., *r*), confidence interval (CI), and stratified scenarios of statistical significance is presented in Table 3.

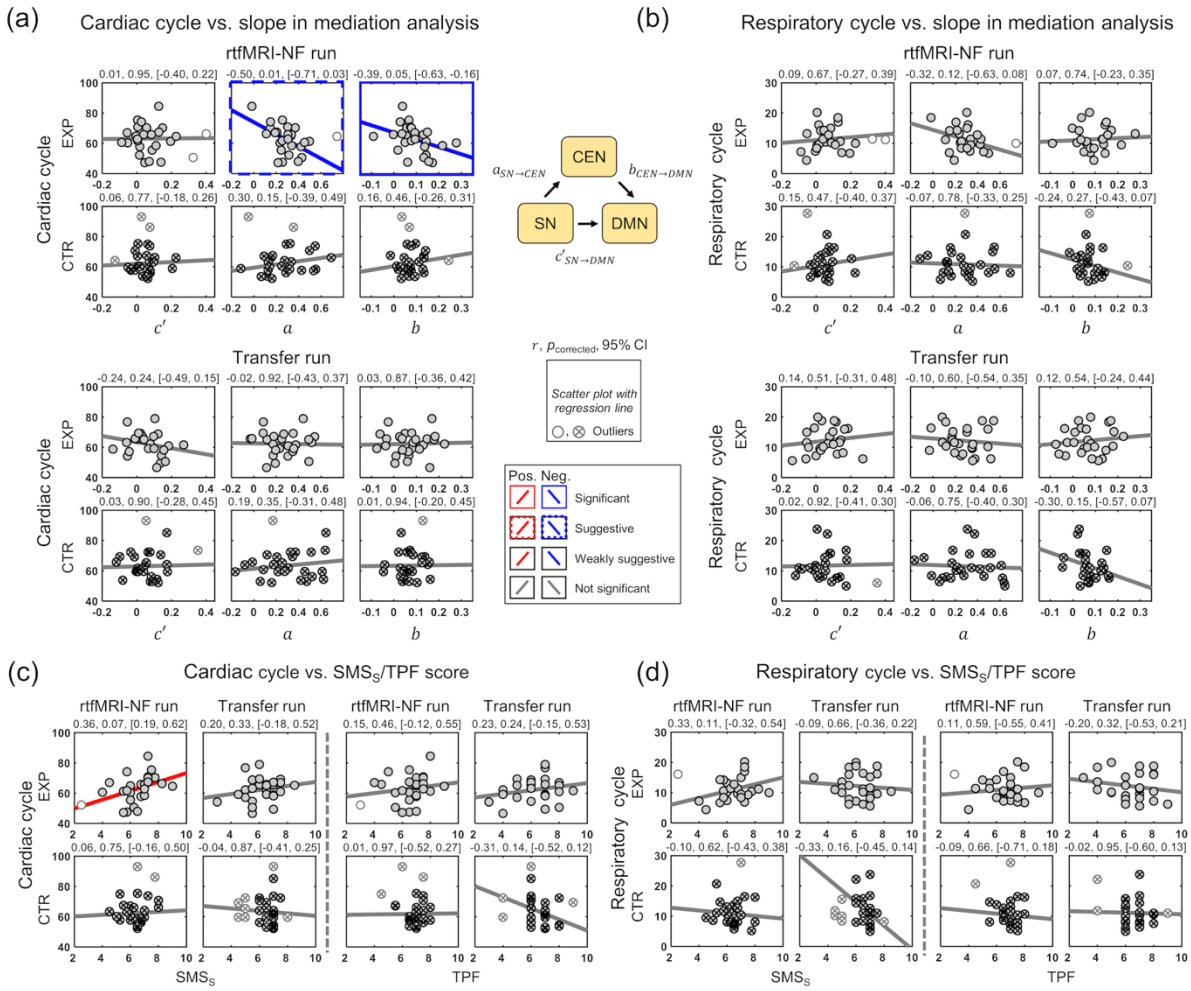

Figure 11. Scatter plots of the cardiac/respiratory cycles and regression coefficients (or slopes; c', a, b) obtained from the mediation analysis (a-b) and the SMS$_S$/TPF scores (c-d) in the rtfMRI-NF and transfer runs. CEN, central executive network, CTR, control group; DMN, default-mode network; EXP, experimental group; Neg., negative; Pos., positive, rtfMRI-NF, real-time fMRI neurofeedback; SN, salience network; SMS$_S$, short version of the State Mindfulness Scale. Detailed information about outliers, p-value correction of correlation coefficient (i.e., r), confidence interval (CI), and stratified scenarios of statistical significance is presented in Table 3.

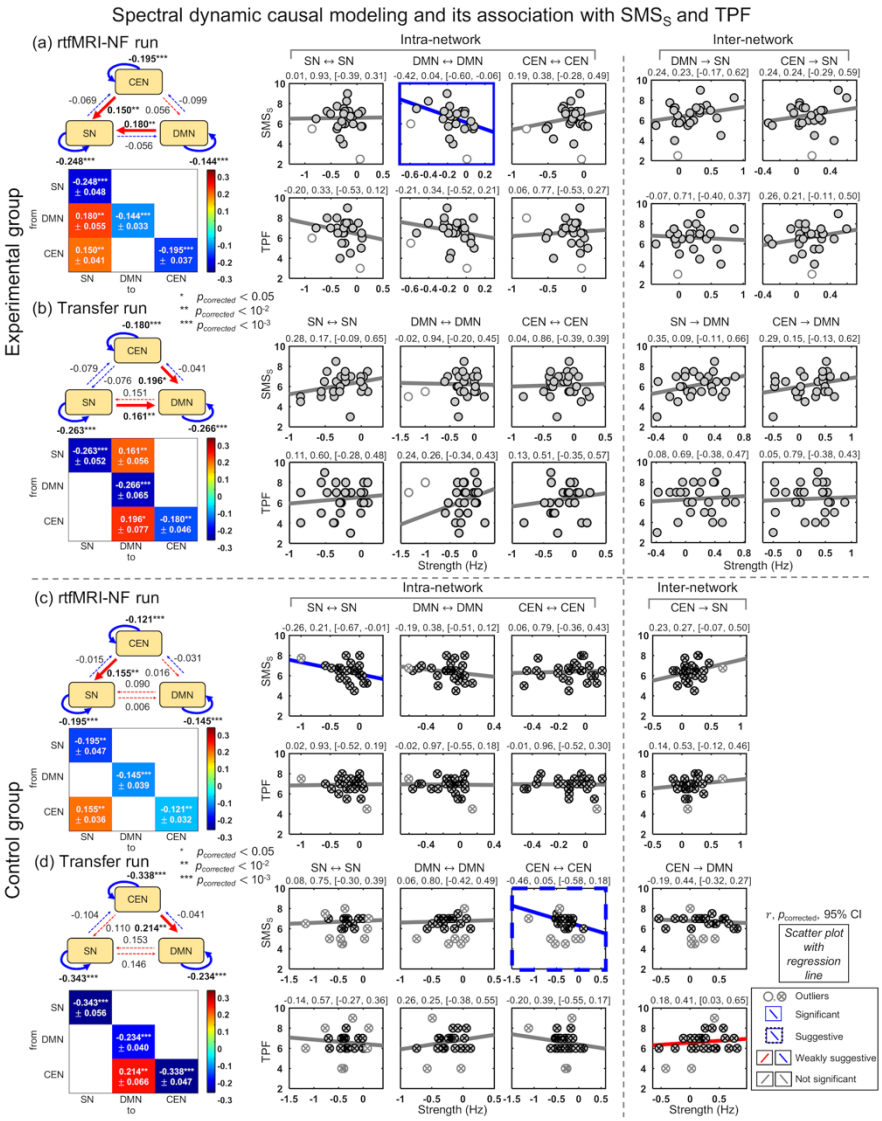

Figure 12. Spectral dynamic causality modeling (spDCM) results and their association with mindfulness (i.e., SMS$_S$) and task-performance feedback (TPF) scores across rtfMRI-NF runs and transfer run in the experimental (a-b) and control (c-d) groups. Diagonal elements indicate self-inhibition in log-scale relative to the prior mean of -0.5 Hz (Almgren et al., 2018). Solid lines in red (excitatory connection) and blue (inhibitory connection) indicate significance ($p < 0.05$), whereas dashed lines indicate non significance ($p > 0.05$). CEN, central executive network; DMN, default-mode network; rtfMRI-NF, real-time fMRI neurofeedback; SMS$_S$, short version of the State Mindfulness Scale; SN, salience network. Detailed information about outliers, *p*-value correction of correlation coefficient (i.e., *r*), confidence interval (CI), and stratified scenarios of statistical significance is presented in Table 3.

Tables

Table 1. Instructions for mindfulness, mind-wandering, and resting-state conditions.

Condition	Instruction
Mindfulness[a]	*Please pay attention to the physical sensation of your breath wherever you feel it most strongly in your body.* *Follow the natural and spontaneous movement of your breath, not trying to change it in any way. Simply pay attention to it.* *If you find that your attention has wandered to something else, gently but firmly bring it back to the physical sensation of your breath.* *Please keep your eyes open.*
Mind-wandering[b]	*Please think about whatever comes to mind and go wherever your mind takes you.* *Follow your thoughts as they arise and let your mind wander, not trying to force your thoughts in any specific direction.* *If you find that a new thought appears, simply allow your attention to shift to this new thought.* *Please keep your eyes open.*
Resting-state[c]	*Please relax and lie still in the scanner while remaining calm and awake.* *Please keep your eyes open.*

[a], text was adapted from (Brewer et al., 2011; Garrison et al., 2013; Meinlschmidt et al., 2016)
[b], text was adapted and extended from (Dickenson et al., 2013)
[c], text was adapted from (Patriat et al., 2013)

Table 2. Sociodemographic information and psychological traits of the participants included in the analyses from the stratified sub-groups based on the sequence-of-condition during the ambulatory training for each of the experimental and control groups.

Categorical Variable	Category	Experimental group (*n*)		Control group (*n*)		Total (*n*)
		MF ⇄ MW (*n* = 13)	MW ⇄ MF (*n* = 13)	MF ⇄ MW (*n* = 16)	MW ⇄ MF (*n* = 10)	
Marital status	Single	11	13	12	9	45
	In a relationship	2	0	4	1	7
Highest degree	High school diploma or equivalent degree	10	11	14	6	41
	Bachelor's degree	1	2	2	4	9
	Master's degree	2	0	0	0	2
Size of household	1	1	2	2	0	5
	2	0	0	0	0	0
	3	0	1	3	1	5
	4	10	7	9	8	34
	5	2	3	2	1	8

Continuous variable	Experimental group (*n*)		Control group (*n*)		Two-way ANOVA (*F; p* from main effect of group, main effect of sequence-of-condition, interaction)
	MF ⇄ MW (*n* = 13)	MW ⇄ MF (*n* = 13)	MF ⇄ MW (*n* = 16)	MW ⇄ MF (*n* = 10)	
Age (years)	25.69 ± 3.84	24.92 ± 2.60	24.75 ± 2.11	25.80 ± 3.22	$F(1,48) = 0.50, 0.09, 2.58$; $p = 0.49, 0.77, 0.12$
Full time education (years)	15.23 ± 2.17	14.46 ± 1.76	14.31 ± 1.20	15.60 ± 1.17	$F(1,48) = 0.00, 0.42, 0.00$; $p = 1.00, 0.52, 1.00$
EHI	95.09 ± 6.15	94.51 ± 7.14	95.01 ± 5.24	94.75 ± 6.72	$F(1,48) = 0.04, 0.02, 0.01$; $p = 0.85, 0.90, 0.95$
BFI-10					
Extraversion	3.31 ± 1.09	3.46 ± 0.72	3.28 ± 1.17	2.85 ± 0.67	$F(1,48) = 1.13, 0.82, 0.05$; $p = 0.29, 0.37, 0.83$
Agreeableness	3.23 ± 0.78	3.04 ± 0.75	3.56 ± 0.75	3.50 ± 0.67	$F(1,48) = 3.78, 0.17, 0.26$; $p = 0.06, 0.68, 0.62$
Conscientiousness	2.88 ± 1.00	3.42 ± 0.70	2.94 ± 0.77	3.25 ± 0.48	$F(1,48) = 0.31, 0.82, 0.05$; $p = 0.58, 0.37, 0.82$
Neuroticism	3.08 ± 0.86	3.19 ± 0.90	2.91 ± 0.95	3.05 ± 0.93	$F(1,48) = 0.64, 0.03, 1.44$; $p = 0.43, 0.87, 0.24$
Openness to Experience	3.81 ± 0.69	3.58 ± 0.73	3.50 ± 0.98	3.65 ± 0.97	$F(1,48) = 0.68, 3.58, 0.06$; $p = 0.42, 0.07, 0.81$
PHQ-9	2.46 ± 2.06	1.08 ± 1.04	2.32 ± 1.40	2.10 ± 1.45	$F(1,47) = 0.77, 0.01, 0.81$; $p = 0.39, 0.97, 0.78$
MAAS	4.78 ± 0.62	4.42 ± 0.46	4.67 ± 0.60	4.71 ± 0.56	$F(1,48) = 0.65, 0.09, 1.43$; $p = 0.42, 0.77, 0.25$
PSS	13.46 ± 4.68	14.54 ± 3.97	12.97 ± 3.75	14.20 ± 3.55	$F(1,48) = 0.29, 0.15, 0.34$; $p = 0.59, 0.70, 0.56$
VAS	3.58 ± 2.11	3.83 ± 1.96	3.28 ± 1.50	4.85 ± 1.89	$F(1,47) = 0.41, 0.15, 0.04$; $p = 0.52, 0.71, 0.85$

n = 52 subjects; 8 out of 60 subjects were excluded due to head motion in the two real-time fMRI neurofeedback runs or the transfer run (average frame-wise displacement (FD) > 0.5). Two-way analysis-of-variance (ANOVA) comparing group (experimental group or control group) and sequence-of-condition (MF ⇄ MW or MW ⇄ MF) was conducted (see the "***Analysis of the behavioral data obtained by the smartphone-based ambulatory training***" in the Supplementary Materials for details). One experimental subject who conducted the ambulatory training under the MF ⇄ MW cycle was identified as an outlier based on the MAD approach regarding both PHQ-9 and VAS.

BFI, Big Five Inventory-10 (John et al., 1991); EHI, Edinburg Handedness Inventory (Oldfield, 1971); MAAS, Mindful Attention Awareness Scale (Brown and Ryan, 2003); MF, mindfulness; MW, mind-wandering; PHQ, Patient Health Questionnaire (Spitzer et al., 1999); PSS, Perceived Stress Scale (Cohen et al., 1983); VAS, Visual Analog scale for Stress perception (0 being not stressed at all, 10 being extremely stressed).

Table 3. Summary of the statistical significance stratified based on both *p*-value from a random permutation[a] and confidence interval (CI) from bootstrapping[b] after the exclusion of potential outliers[c]. Unlike a previous approach (Terhune et al., 2014), a "potentially weakly suggestive" was also considered when the CIs did not include a small positive value $\varepsilon \triangleq 0.05$ or $-\varepsilon$ even though 0 was in the CIs.

	$0 \notin CI$	$0 \in CI$	
$p \leq 0.05$	Significant	Suggestive	
$p > 0.05$	Weakly suggestive	$\varepsilon \notin CI$ *or* $-\varepsilon \notin CI$	$\varepsilon \in CI$ *or* $-\varepsilon \in CI$
		Potentially weakly suggestive	Not significant

[a] Total of 10,000 random permutations using randomized indices of participants were conducted and the *p*-value was obtained from the corresponding null distribution (Groppe et al., 2011; Manly, 2006).

[b] The 95% confidence interval (CI) of correlation coefficients was obtained from 10,000 cycles of bootstrapping with replacement (Pernet et al., 2013; Terhune et al., 2014).

[c] Refer to the section, "***Definition of outliers based on median absolute deviation (MAD)***" in the Supplemental Material for details.

2.4 Publication 4: Personalized prediction of smartphone-based psychotherapeutic micro-intervention success using machine learning

Full reference: G. Meinlschmidt, M. Tegethoff, A. Belardi, E. Stalujanis, M. Oh, E. K. Jung, H.-C. Kim, J.-H. Lee, S.-S. Yoo, and J.-H. Lee. Personalized prediction of smartphone-based psychotherapeutic micro-intervention success using machine learning. *Journal of Affective Disorders*, in press. doi:10.1016/j.jad.2019.11.071

Manuscript

Personalized prediction of smartphone-based psychotherapeutic micro-intervention success using machine learning

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Introduction

Mental disorders are a major challenge for public health, leading to premature mortality and increasing the risk of and interfering with the treatment of physical diseases, with huge economic costs (Gustavsson et al., 2011; Kleinman et al., 2016; Prince et al., 2007; Tegethoff et al., 2015; Tegethoff et al., 2016; Whiteford et al., 2013). It is not surprising, therefore, that strategic research initiatives clearly point to the urgent need for new interventions and evidence-based prevention approaches (Collins et al., 2011).

The goal of personalized medicine is to target healthcare to the individual patient (Collins and Varmus, 2015). Most efforts have so far been devoted to tailoring drugs to the person's genomic profile; however, work has meanwhile expanded to also tailoring non-pharmacological treatments to a patient's individual molecular setup (Eley et al., 2012) and to tailoring treatments based on other than genomic information, including brain signatures (Kim et al., 2015) and contextual information (van Os et al., 2013).

New technologies, including eHealth, mHealth, and computational approaches may open promising opportunities towards personalized interventions (Mikolasek et al., 2017; Zeevi et al., 2015). For example, mobile phone-based technologies are used to collect various contextual data at high sampling frequency in a person's real-world environment (Asselbergs et al., 2016; Mohr et al., 2017) and they are increasingly used in the context of mental health interventions (Firth et al., 2017; Menon et al., 2017). Moreover, machine learning-based computational methods, providing data-driven accurate predictions on pre-defined research questions, are on the rise in mental health research (Iniesta et al., 2016). As compared with conventional statistical methods that allow for predictions primarily at group-level, machine learning-based algorithms provide results at the level of an individual subject. One important clinical outcome in the context of

mental health addressed with machine learning-based approaches is the prediction of treatment response (Passos et al., 2016). The first available studies encourage such new computational methods in the context of differential therapy indication (Connor et al., 2007; Costafreda et al., 2009; Doehrmann et al., 2013; Gao et al., 2018; Hahn et al., 2015; Hoogendoorn et al., 2016; Mansson et al., 2015); however, evidence on the utility of machine learning-based approaches in the prediction of the response to i) preventive mental health interventions that are ii) based on new technologies is as yet lacking.

The main aim of this study was to explore the utility of machine learning algorithms based on contextual information that would enable the prediction of smartphone-based psychotherapeutic micro-intervention success in terms of mood amelioration.

Methods

The study has previously been described in detail (Meinlschmidt et al., 2016). In brief, the data presented here were collected within a randomized trial, registered at ClinicalTrials.gov (Identifier: NCT01921088), available at https://clinicaltrials.gov/ct2/show/NCT01921088. The Institutional Review Board of Korea University approved the study protocol. All subjects gave written informed consent in accordance with the Declaration of Helsinki. The study was conducted between August and October 2013 at the facilities of Korea University, Seoul, Republic of Korea (Resource Identifier (RRID): SCR_013726).

Subjects were recruited from the student body of Korea University via advertisements posted on the university website and a local bulletin board. Inclusion criteria were: i) being adult male (18-65 years), ii) right-handed (as assessed using the Edinburgh Handedness Inventory (Oldfield, 1971)), iii) having no color-blindness (as assessed using the Ishihara test for color-blindness (Ishihara and Force, 1943)), iv) having no history of cardiovascular or neurological diseases or mental disorders (as assessed by self-report), and v) reporting sufficient English language skills to follow the experimental instructions and vi) having at least minimal familiarity with smartphone-use to carry out the micro-interventions.

On each of 13 consecutive days, subjects conducted a smartphone-based psychotherapeutic micro-intervention guided by a short video-clip (duration: approx. 4 min 40 s), scheduled at any time between 0800h and 0300h the next day. For each day, subjects chose one out of four psychotherapeutic techniques: i) viscerosensory attention (i.e. shifting attention towards versus away from bodily sensations), ii) emotional imagery (i.e. imagining emotionally positive, negative or neutral situations), iii) facial expression (i.e. making different emotional facial expressions), or iv) contemplative repetition (i.e. repeating a short simple sentence or word over

and over again, or slowly and repeatedly counting from 1 to 10). All four psychotherapeutic techniques have been shown to be related to changes in mood (Holmes et al., 2006; Kleinke et al., 1998; Lane et al., 2007; Pollatos et al., 2015), with potential for the treatment of mental disorders (Holmes et al., 2007; Ito et al., 2001; Lin et al., 2015; Orme-Johnson and Barnes, 2014). Additionally, participants were allowed to use any other individual technique that they felt would be helpful. Before and after the micro-intervention, subjects electronically filled in the 12-item Multidimensional Mood State Questionnaire (MDMQ), to provide information on their current mood. The MDMQ is the English version of the German *Mehrdimensionaler Befindlichkeitsfragebogen* (MDBF), a well-established tool for the assessment of current mood, with very good psychometric properties, especially suited for repeated measures within short intervals (Steyer, 2014; Steyer et al., 1997). This study focuses on the dimension ranging from good to bad (GB), for which a score was calculated, ranging from 4 to 24. High scores suggest positive affectivity.

The smartphone-based micro-interventions were conducted using EFS Survey 10.0 (Questback GmbH, Berlin, Germany).

Data were checked for distribution properties and verified normality by inspecting histograms and quantile-quantile plots. For descriptive analyses, means and standard deviations for continuous normally distributed variables and absolute and relative frequencies for categorical variables were calculated with categories outlined in Table 1.

-- Insert Table 1 here --

A positive response to a specific micro-intervention (i.e., a ‘successful’ micro-intervention) was defined as an increase in mood indicated by a higher value in the GB dimension of the MDMQ after the intervention with respect to the measures acquired before the intervention. We

calculated the success rate (or response rate) to the micro-intervention as relative frequency of successful micro-interventions.

To predict micro-intervention success, the following variables were used as predictors: mood change from pre- to post-micro-intervention on the previous intervention day for all three dimensions (GB, awake-tired (AT), calm-nervous (CN)) and mood score for dimensions AT and CN at pre-micro-intervention on the same intervention day. Predictions were partly based on indicators from the previous intervention day, and such information was not available for the first intervention day, thus we only predicted success of micro-interventions conducted on intervention days 2 to 13. For the analyses, we included all subjects that took part in at least 3 micro-intervention sessions. To account for missing data, we applied mean imputation using all available values for the given subject.

A machine learning approach based on random forests (RFs) was applied to predict whether a certain micro-intervention session was successful. In a second step, an approach using generalized linear mixed-effects models (GLMM) was applied to relate the main results to a more conventional approach. Both approaches were used in a supervised learning classification problem (depicted in Figure 1), where the goal was to predict each session's success (outcome 'successful micro-intervention'; dichotomous) using the above-mentioned predictor variables.

-- Insert Figure 1 here --

Our RF approach was based on the algorithm (Bürgin and Ritschard, 2015) for building tree-structured fixed-effects predictor functions in mixed-effects logistic regression models. The RF implementation of this algorithm has recently been provided (Bürgin, 2017). RFs were calculated considering the above-mentioned predictors as potential partitioning variables for the trees. Additionally the person-level variable 'subject' (categorical) as well as the higher-level variable

‘micro-intervention day’ (dimensional, day 2 to 13) were entered into the model, with random intercept and random slope parameters for subject over day.

For the final RF model, parameters were optimized starting with the default parameter configuration, as previously reported (Bürgin and Ritschard, 2015; Bürgin, 2017); from there, we modified one parameter at a time, until local maxima of prediction quality indicators were reached, resulting in the following parameters: number of trees B = 100, minimum node size $N0$ = 20, number of randomly selected combinations of nodes and moderators $mtry$ = 15, maximum number of steps for growing each tree $maxstep$ = 40, training error reduction minimum for a split to be used in the model $D_{min}/mindev$ = 1.5, number of times the coefficient constancy tests are repeated in each iteration $nimpute$ = 1.

The GLMM approach consisted of generalized linear mixed-effects models (Singer and Willett, 2003) with a logit link function. For these models, each of the above-mentioned predictors were entered into the linear-mixed-effect models as fixed effects. Further, the person-level variable ‘subject’ (categorical), as well as the higher-level variable ‘micro-intervention day’ (dimensional, day 2 to 13) were entered into the model, as random effect with random intercept and random slope parameters for subject over day.

To enable training, evaluation, and comparison of the models, the total sample of micro-intervention sessions was randomly split into a training subsample and a test subsample, using a ratio of about 80:20. Thereby two different splitting strategies were applied, one to estimate the performance of the prediction within the same group of subjects and one to estimate the performance of the prediction for a different group of subjects. To estimate the quality of the prediction within the same group of participants, the sessions were split within each participant 9:3 (0.75 in training subsample), so that sessions from each participant contributed to the training

(9 sessions) as well as the test (3 sessions) subsample. To estimate the performance of the prediction for a different group of participants, the total sample of participants was split 22:5 (approx. 0.81 in training subsample), contributing all sessions of each participant to either the training or the test subsample.

The training subsample was used to estimate the models and the separate test subsample was used to predict the success of the micro-interventions. Comparing these predictions with the true success allowed estimating the quality of the predictions (see Figure 1).

As indicator of the quality of the predictions, three metrics were estimated: First, the positive predictive value (PPV) was calculated, here defined as the proportion of truly successful micro-interventions out of micro-intervention sessions for which the model predicted success. Notably, PPVs provide information on success rates that would be obtained when restricting the application of micro-interventions to sessions that are expected to be successful. However, PPVs do not reflect sessions for which no success is predicted. Hence, second, the rand accuracy (ACC) was calculated, defined as the number of sessions correctly predicted as successful or non-successful relative to the total number of sessions. However, this accuracy indicator is dependent on the initial success-rate. Therefore, third, also the Matthews' Correlation Coefficient (MCC) was calculated– a dichotomous form of the Pearson correlation coefficient as a more balanced measure of the quality of binary classifications – commonly used in machine learning (Power, 2011). For these metrics, 95% confidence intervals (CIs) were calculated i) for PPV, using the functionality in the R package 'bdpv', based on a procedure described elsewhere (Mercaldo et al., 2007), ii) for ACC, based on an exact binomial test via the R package 'caret', and iii) for MCC, using the method described by Fleiss and colleagues (p. 135, equation 6.122) (Fleiss et al., 2004).

These quality indicators may arbitrarily vary due to the random splitting of the data. Hence, the splitting, training, and evaluation of the prediction models were repeated 100 times for both models and here report the quality indicators calculated after averaging the confusion matrices within each model across these 100 repetitions. Further, to exclude that this random splitting of the data may have resulted in chance findings suggestive of differences in quality estimators, respective statistical inference testing was conducted, comparing the quality estimators of the four procedure combinations: i) RF approach within-subject sampling, ii) RF approach between-subject sampling, iii) GLMM approach within-subject sampling, and iv) GLMM approach between-subject sampling. First, we tested for differences in prediction quality (PPV, ACC, and MCC) across all four procedure combinations, by calculating a Friedman test, followed by Nemenyi post-hoc pairwise comparisons that account for family-wise error.

All tests were two-tailed and the significance level was set at 0.05, if not otherwise specified. The statistical software package R (version 3.3.2 and above) (R Core Team, 2015) was used for all data analyses, visualizations, and statistical testing. Besides base R functions we used additional specific packages as follows: to conduct the linear mixed-effect models, ‘lme4’ (Bates et al., 2014) and ‘optimx’ (Nash and Varadhan, 2011), for data preparation and descriptive statistics ‘car’ (Fox and Weisberg, 2011), ‘dplyr’ (Wickham and Francois, 2015), ‘Hmisc’ (Jr Frank and Dupont, 2015), ‘lmerTest’ (Kuznetsova et al., 2015), ‘pastecs’ (Grosjean and Ibanez, 2014), ‘tidyr’ (Wickham, 2015), and ‘haven’ (Wickham and Miller, 2015), for data visualisations ‘ggplot2’ (Wickham, 2016); for some qualifier metric calculations ‘caret’ (Kuhn, 2017) and ‘bdpv’ (Schaarschmidt, 2014), for the Friedman tests and Nemenyi post-hoc tests ‘PMCMR’ (Pohlert, 2014), and for the RF models ‘vcrpart’ (Bürgin, 2017).

Results

The flowchart of participants is provided in Figure 2. From the 31 subjects included in the study, one participant did not show up on experiment day 1 and hence neither received instructions for nor participated in any smartphone-based micro-intervention. Three other subjects did participate in less than three micro-intervention sessions (one subject participated in 1 session and two subjects participated in 2 sessions) and were hence excluded from further analyses. All subjects were males of Korean nationality. Characteristics of the study sample on which the analyses are based ($N = 27$) are provided in Table 1.

The 27 subjects contributed a total of 324 smartphone-based micro-intervention sessions (day 2 to 13). Out of these sessions, mood improved in 137 sessions (42.3%), remained unchanged in 94 sessions (29%) and worsened in 93 sessions (28.7%). Hence, overall, there was an initial micro-intervention success rate of 42.3%.

PPVs, ACCs, and MCCs and their 95% CIs of the predictions, calculated from mean confusion matrix values, across the four procedure combinations i) RF approach within-subject sampling, ii) RF approach between-subject sampling, iii) GLMM approach within-subject sampling, and iv) GLMM approach between-subject sampling are depicted in Figure 3. PPVs of the RF approach with between- and within-subject sampling schemes were significantly higher than the initial success rate of 42.3%. However, the GLMM approach resulted in predictions significantly better than the initial success rate only within subjects but not between subjects.

The omnibus tests showed a statistically significant main effect for the four compared models (RF and GLMM approaches with between- and within-subject sampling schemes) for all three quality estimator metrics (PPV, ACC, MCC), indicating that it is highly unlikely that our random splitting of the data into training and test samples may have resulted in chance findings that

would incorrectly suggest differences in quality estimators (see Table 2). In line with this, Friedman-Nemenyi pairwise post-hoc tests indicated significant differences for all metrics when comparing i) the RF and the GLMM approach with within-subject sampling, ii) and the RF and the GLMM approach with between-subject sampling (see Table 2).

-- Insert Figure 2 here --

-- Insert Figure 3 here --

-- Insert Table 2 here --

Discussion

The main aim of this study was to explore the utility of a machine learning-based random forest algorithm using contextual information for predicting smartphone-based psychotherapeutic micro-intervention success in terms of mood amelioration. Our findings provide evidence for such predictability within the same subjects as well as for different subjects.

Our results on the predictability of smartphone-based psychotherapeutic micro-intervention success add to the wealth of previous evidence on factors predicting the outcome of conventional psychotherapy based on conventional statistical approaches (Colvonen et al., 2017; Knaevelsrud and Maercker, 2006; Luborsky et al., 1971; Meuret et al., 2015; Riper et al., 2014; Scherer et al., 2017; Schneider et al., 2015; Schottke et al., 2016; Styla, 2015; Wiltink et al., 2016) as well as to the fewer studies investigating the utility of machine learning-based approaches in the prediction of the response to pharmacological (Chekroud et al., 2016; Kautzky et al., 2017; Koutsouleris et al., 2016) or other psychiatric (Redlich et al., 2016) treatments in persons with mental disorders. To date, there is also first evidence on the utility of machine learning-based predictions of the response to conventional psychotherapeutic interventions in persons with mental disorders (Connor et al., 2007; Costafreda et al., 2009; Doehrmann et al., 2013; Hahn et al., 2015; Hoogendoorn et al., 2016; Mansson et al., 2015) and to smartphone-based intervention approaches in the promotion of nutrition and cardiovascular health (Alshurafa et al., 2017). While most of the former studies on the success of conventional psychotherapy focused on brain data as predictors, the available research on the prediction of smartphone-based intervention success took advantage of dynamic contextual information. In line with a former study on smartphone-based health support systems, which covered predictors in a time frame of one month during the first month of intervention (Alshurafa et al., 2017), we could show in an even

higher temporal resolution that factors related to the intervention day and the day before were predictive of micro-intervention success.

This study has several important strengths, among others (Meinlschmidt et al., 2016) using mixed effects RF to account for the nested nature of the data, as one of the most recent methodological advances in RF analyses (Bürgin and Ritschard, 2015). Some limitations of the study protocol have been discussed previously, including use of English study material in native Korean speakers with, however, excellent knowledge of written English (Meinlschmidt et al., 2016). Moreover, first, the RF approach does not allow firm conclusions about the exact contribution of each factor to the algorithm's predictions, a limitation ('the machine learning black box') resulting in tension between accuracy and interpretability (Cabitza et al., 2017). Even though strategies to alleviate this tension, such as partial dependence plots (Hastie et al., 2017) may help identify the relevance of factors, such procedures have also been discussed to be misleading due to higher-order interactions (Zeevi et al., 2015). Second, we only included a limited number of predictors, which was necessary to prevent overfitting, as we compared the RF of tree-based mixed-effects logistic regression models for longitudinal data with more conventional general linear models, the latter being especially sensitive to overfitting. Third, subjects chose different psychotherapeutic techniques but due to small subsample sizes we did not compare whether predictability differed between techniques.

Future studies should include further, stable (trait) as well as situational or contextual dynamic, factors that have previously been attributed to the prediction of treatment outcomes, including stable psychological features or biomarkers (Meuret et al., 2015; Scherer et al., 2017). Moreover, future studies should shed some further light on the usability of the here applied machine learning approach in the context of differential treatment indication and predict for example

which intervention will work best for a certain person at a certain time and in a certain context. From a methodological point of view, alternative approaches and techniques for parameter optimization and classifier selection (see Amancio et al., 2014; Rodriguez et al., 2019) may have the potential to further increase the precision of the prediction models. Of note, our results may not be generalizable to women, children, elderly, and persons with mental disorders or physical diseases, with those seeking psychotherapeutic interventions being on average older than our sample. Hence, it would, for example, be interesting to study the predictability of treatment success in a larger patient sample. Further, self-report assessment of microintervention success could be complemented by clinician-based microintervention success assessments that are less prone to biases. Finally, it may generally be worthwhile to test the machine learning-based approach of personalizing treatment indication in other fields of application, for example in contexts of digital education or pain research, with the corresponding adaptations in training contents and outcome variables to be trained.

Our findings may have different implications. First, mental disorders and the rate of non-responders to psychotherapeutic interventions remain a relevant challenge for public health (Steinert et al., 2016; Wykes et al., 2015). The precision medicine approach deals with this task and pursues the development of tailored interventions (Collins and Varmus, 2015). In this context, tailored decisions about the suitability of a treatment may help save resources of patients and health personnel and prevent inappropriate steps of care. Patients may either benefit from stronger treatment effects or from a greater compliance. Second, the advancement of approaches to prevent mental disorders and the implementation of early interventions is one central research strategy to improve mental health worldwide (Collins et al., 2011). Bringing the precision medicine concept to the field of mental health promotion may be a wise next step to advance

disease prevention. Third, the rather equal performance of within- and between-subject subsampling schemes with our RF approach points to a flexible applicability of the prediction scheme to (comparable) subgroups in which the algorithm has not been trained.

Taken together, we were able to train a machine learning-based algorithm that predicted the individual success of and thereby has the potential to increase the response rate to a smartphone-based psychotherapeutic micro-intervention in terms of mood amelioration. This approach is in line with the precision medicine initiative and may represent a promising tool to tailor decisions about the suitability of psychotherapeutic micro-interventions in real-world settings to individual needs.

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Table 1. Characteristics of the study sample (*N* = 27)

Categorical variables			
Variable	**Category**	***n***	**(%)[a]**
Marital status			
	Single	20	(74%)
	In a relationship	7	(26%)
Highest degree			
	High school or equivalent	24	(89%)
	Bachelor's degree	3	(11%)
Size of household (including participant)[b]			
	1	1	(4%)
	2	0	(0%)
	3	1	(4%)
	4	22	(85%)
	5	2	(8%)
"I am very experienced in using smartphones"			
	Strongly agree	7	(26%)
	Agree	14	(52%)
	Neutral	4	(15%)
	Disagree	1	(4%)

	Strongly disagree	1 (4%)

Continuous variables

Variable (unit)	Mean	(*SD*)	Range [min, max]
Age (years)	24.32	(2.27)	[19.75, 28.70]
Fulltime education (years)	15.15	(1.38)	[12, 18]

[a]*Percentages may not total 100 due to rounding;* [b]*Information from one subject missing;*

Abbreviations: max, maximum; min, minimum; SD, standard deviation.

Table 2. Statistical comparisons between prediction models

Omnibus tests: main effect comparing the four applied prediction models[a]			
Quality estimator metric	***χ2***	***df***	***p***
PPV	114.32	3	< .001
ACC	167.3	3	< .001
MCC	174.9	3	< .001

Post-hoc tests: Friedman-Nemenyi pairwise post-hoc tests, comparing the RF with the GLMM approach			
Within or between subject sampling	**Quality estimator metric**	***Z***	***p***
Within subject sampling	PPV	7.67	< .001
Within subject sampling	ACC	8.99	< .001
Within subject sampling	MCC	8.91	< .001
Between subject sampling	PPV	11.31	< .001
Between subject sampling	ACC	14.02	< .001
Between subject sampling	MCC	13.40	< .001

[a]*RF and GLMM approaches with between- and within-subject sampling schemes.*

Abbreviations: ACC, rand accuracy; df, degree of freedom; GLMM, generalized linear mixed-effects model; MCC, Matthew's correlation coefficient; PPV, positive predictive value; RF, random forest.

Figures

Title Figure 1: Outline of the RF-based supervised learning classification problem and prediction quality estimation approach.

Caption Figure 1: [a]RF-based prediction algorithms, using tree-structured fixed-effects predictor functions in mixed-effects logistic regression models; [b]Prediction quality indicators: positive predictive value (PPV), rand accuracy (ACC), and Matthew's correlation coefficient (MCC). [c]We repeated the splitting, training, and evaluation of the prediction model 100 times for each model and calculated the quality indicators after averaging the confusion matrices for each model across these 100 repetitions. *Note:* We applied two different subsampling schemes: 1) a between-subject subsampling scheme, in which the training subsample and test test subsample consisted of separate participants ('between subject split'), and 2) a within-subject subsampling scheme, in which the training subsample and test subsample consisted of different sessions per participant ('within subject split'). *Abbreviations: B, number of trees; i, number of microintervention sessions in the training subsample; n, no; N, number of microintervention sessions; no, number; RF, random forest; y, yes;*

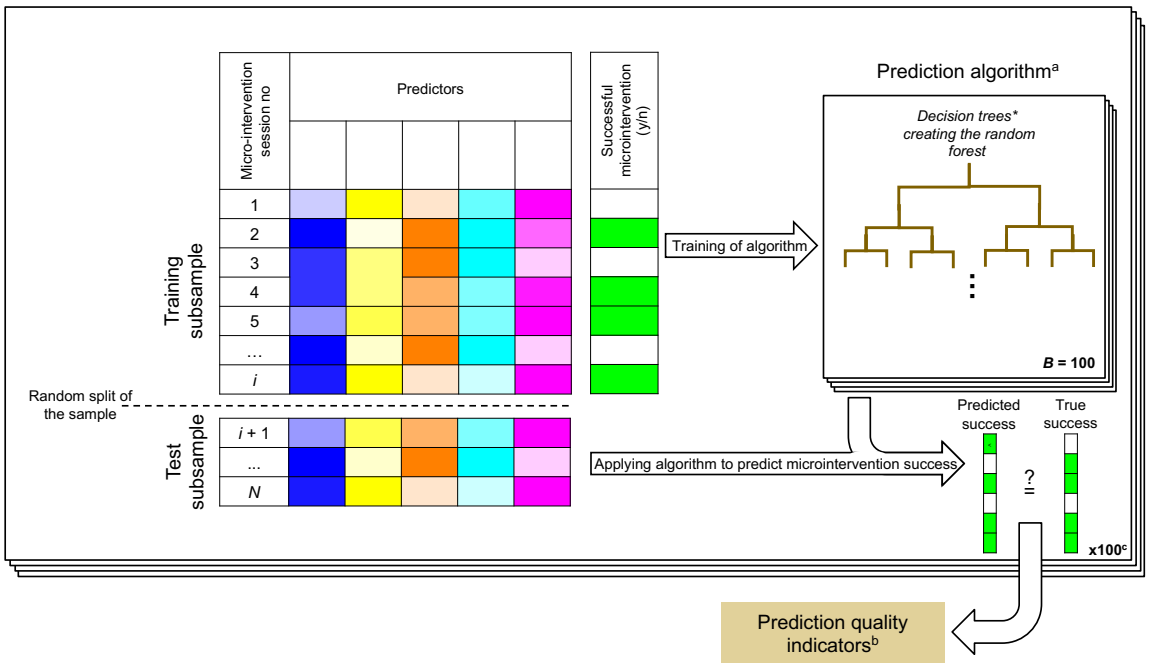
Title Figure 2: Participant flow through study.

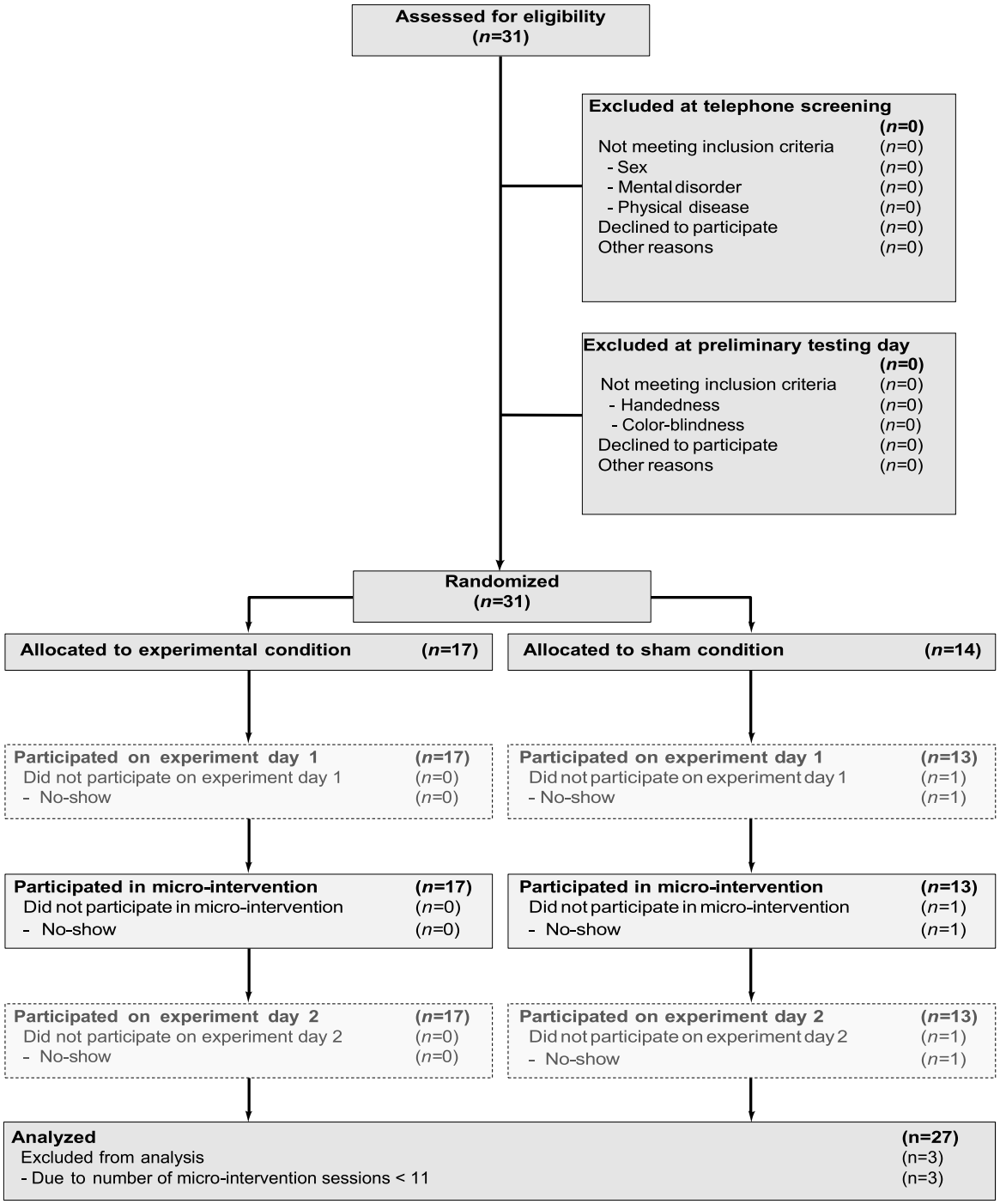
Title Figure 3: Quality indicators of prediction of intervention success across prediction models (means and 95% CIs).

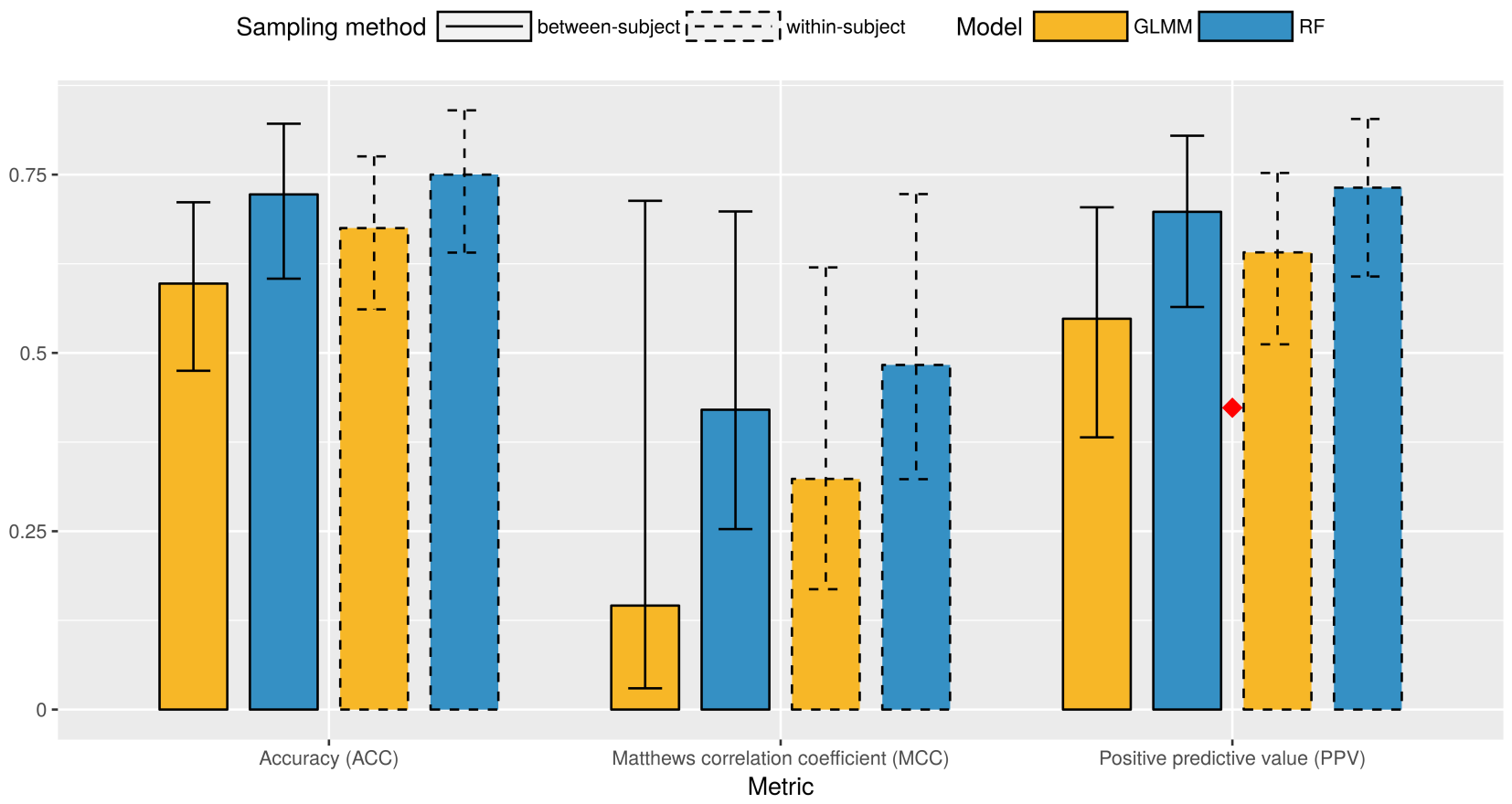
Caption Figure 3: *Note:* The red diamond indicates the initial response rate (42.3%). Results based on 324 micro-intervention sessions. We applied two different subsampling schemes: 1) a

between-subject subsampling scheme, in which the training subsample and the test subsample consisted of separate participants, and 2) a within-subject subsampling scheme, in which the training subsample and test subsample consisted of different sessions per participant.

Abbreviations: ACC, rand accuracy; CI, confidence interval; GLMM, generalized linear mixed-effects model; MCC, Matthew's correlation coefficient; PPV, positive predictive value; RF, random forest.


Micro-intervention session no
Predictors
Successful microintervention (y/n)
Training subsample
1
2
3
4
5
…
i
Random split of the sample
Test subsample
i + 1
...
N
Training of algorithm
Prediction algorithm[a]
Decision trees* creating the random forest
B = 100
Applying algorithm to predict microintervention success
Predicted success
True success
?
=
x100[c]
Prediction quality indicators[b]


Assessed for eligibility
(n=31)
Excluded at telephone screening
(n=0)
Not meeting inclusion criteria (n=0)
- Sex (n=0)
- Mental disorder (n=0)
- Physical disease (n=0)
Declined to participate (n=0)
Other reasons (n=0)
Excluded at preliminary testing day
(n=0)
Not meeting inclusion criteria (n=0)
- Handedness (n=0)
- Color-blindness (n=0)
Declined to participate (n=0)
Other reasons (n=0)
Randomized
(n=31)
Allocated to experimental condition (n=17)
Allocated to sham condition (n=14)
Participated on experiment day 1 (n=17)
Did not participate on experiment day 1 (n=0)
- No-show (n=0)
Participated on experiment day 1 (n=13)
Did not participate on experiment day 1 (n=1)
- No-show (n=1)
Participated in micro-intervention (n=17)
Did not participate in micro-intervention (n=0)
- No-show (n=0)
Participated in micro-intervention (n=13)
Did not participate in micro-intervention (n=1)
- No-show (n=1)
Participated on experiment day 2 (n=17)
Did not participate on experiment day 2 (n=0)
- No-show (n=0)
Participated on experiment day 2 (n=13)
Did not participate on experiment day 2 (n=1)
- No-show (n=1)
Analyzed (n=27)
Excluded from analysis (n=3)
- Due to number of micro-intervention sessions < 11 (n=3)


Sampling method
between-subject
within-subject
Model
GLMM
RF
0.75
0.5
0.25
0
Accuracy (ACC)
Matthews correlation coefficient (MCC)
Positive predictive value (PPV)
Metric

Conflict of interest

Personalized prediction of smartphone-based psychotherapeutic micro-intervention success using machine learning

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Conflicts of Interest: None. GM has been acting as consultant for Janssen Research & Development, LLC.

Author statement

Personalized prediction of smartphone-based psychotherapeutic micro-intervention success using machine learning

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Author contributions: GM, MT, SY, and JL designed the study; GM, MT, AB, ES, and JL prepared the study material and data acquisition; ES, MO, EJ, HK, and JL recruited participants and acquired the data; AB and ES entered the data and prepared it for statistical analyses; GM,

AB, and ES analyzed the data; GM, MT, AB, and JL interpreted the data; GM and MT wrote the first draft of the manuscript; GM, MT, ES, AB, MO, EJ, HK, SY, and JL critically revised the manuscript for important intellectual content; MT obtained funding; All authors gave final approval of the manuscript version to be published and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

3 Discussion

3.1 Results in context

Publication 1 found mixed results for the main experiment hypothesis, that rtfMRInf could help people to actively modulate aspects of their stress response (brain activity and blood pressure reaction) to an acute stressor (a cognitive task). Time series analyses of the brain activity showed that the stress-related increase of neural activity in the ACC was lower in the experimental compared to the control condition. Experimental control participants also had lower ACC and IC activity during trials in which they could decide which mental strategy they wanted to use to lower their activity in these regions (without a stressor present) compared to trials in which they had to use a specific strategy. None of these findings transferred to the blood pressure data. Generally, the responses to the stressor were rather small and diminished over repetition of the task during the experiment. These findings are a first indication that it is possible to volitionally modulate specific biological factors of the stress response with the help of rtfMRInf in regard to the neural activity. The question remains, whether such training can generalize to how people respond to future stressors, especially whether such training can lead to long-term changes in how people deal with a stressor as it comes up during life. If that was the case, even expensive interventions — as such rtfMRInf sessions are — might become cost-effective. Going back to the biological foundation of neural plasticity, we have to keep in mind that while changes can occur rather quickly, after only hours or days of training, they are also quickly undone again when training stops [Classen et al., 1998]. The results also raise the question how far this modulation goes, since it did not transfer to our cardiovascular measure (blood pressure).

In publication 2 we found increases in self-reported arousal linked to the use of rtfMRInf. Participants also reported being in a worse mood and more tired after the experiment than before, unrelated to the neurofeedback condition. These findings went against our aim of decreasing the stress response in regard to psychological measures. Our assumption is that the multitasking aspect of the experiment might have led to a higher cognitive demand on the experimental participants in comparison to the control participants, if they realized whether the feedback signal they received was real or sham.

Publication 3 found an association between a simple mindfulness task and the interplay between three major neural networks, the default-mode network (DMN), the central executive network (CEN), and the salience network (SN). Furthermore, the neurofeedback training was significantly correlated with the activity in this functional feature of mindfulness, indicating that participants were able to modulate this complex

activity volitionally. This inspires further research into using much more complex feedback signals that combine the activity from several brain areas (functional connectivity) or even from several networks. This seems a logical next step in neurofeedback research, given that complex mental functions are likely to activate multiple functionally connected regions throughout the brain [van den Heuvel and Hulshoff Pol, 2010]. If we want to optimally train such functions, we must try to feed back a signal that resembles the neuronal activity behind it as accurately as possible. Several studies went already beyond using simple activity signals from one or several specific regions and worked with functional connectivity between regions [Koush et al., 2013, Zilverstand et al., 2014, Megumi et al., 2015, Kim et al., 2015]. The use of such complex interactions between major neural networks, however, is still in its early stages.

In an earlier publication, we had reported increase in self-reported mood from before to after SBI sessions [Meinlschmidt et al., 2016]. Publication 4 showed that data from an SBI can potentially be used during the course of the intervention to predict when a new training session is appropriate or not (i.e. when it is unlikely to help). This is a step in the direction of tayloring SBIs to people while they are undergoing the intervention, using data continuously gathered during the intervention (e.g. through logged data of the user, or even meta-information about for example the time when a person used the intervention). It opens a broad field of possible future investigations which might eventually lead to wide dissemination of SBIs in combination with or in place of face-to-face therapy.

Taken together, the results of the here-presented four publications suggest that rtfMRInf might help people to gain control over their individual stress-response as indicated in their stressor-related neuronal activity, while being exposed to a stressor. Since the effects did not transfer to a cardiovascular measure (blood pressure) and self-reported psychological measures connected to stress, we are cautioned to interpret these findings carefully and further research is needed to establish whether such neurofeedback training can become a welcome addition to the range of available interventions to prevent or treat stress-related disorders. It further shows that the use of more complex neural activity for the neurofeedback signal is likely to improve this approach in general. In regard to SBIs, our findings further support the notion that data recorded during a multi-session intervention can be used to improve personalization of future interventions.

3.2 Implications and future research

The landscape of available treatments for widespread mental health issues, like stress-related disorders, is broadening with the rise of technological advances. While the underlying ideas remain predominantly rooted in CBT and other established approaches (like relaxation techniques), they now allow treatment taking place outside of the traditional setting of one therapist and patient talking with each other in a room

(face-to-face therapy) and allow tailoring interventions under the use of personal biological and behavioral data more precisely to a patient. I think it is unlikely that there will ever be a one-size-fits-all solution to any mental disorder or difficulty and therefore the combination of such new methods with personal data is likely to become a key player in how we treat mental disorders.

As far as I know, we are the first to report the use of rtfMRInf to target the stress response, but there is a lot of potential for neurofeedback-based interventions in combination with traditional psychotherapy to help patients deal with their disorders. Some published literature already found evidence for rtfMRInf to support psychotherapy. MacDuffie et al. [2018] for example already reported rtfMRInf as succesfully supporting psychotherapy after only one session in depressive patients. In regard to the modulation of stress, there is still no research published on rtfMRInf targeting the stress response (apart from the publications in this thesis). However, a symposium abstract from 2017 reported that EEG-based neurofeedback training of the amygdala decreased stress vulnerability in a sample of 160 healthy soldiers [Keynan and Hendler, 2017]. For future research, the next steps need to clarify whether and in what degree rtfMRInf or other forms of neurofeedback can help healthy subjects modulate their stress response. It will be especially important to investigate whether also cardiovascular or endocrine aspects of the stress response might be modulated and under which circumstances this is possible. Psychological factors of the stress response might also be further scrutinized, especially in regard to our conflicting findings in publication 2, where participants reported higher arousal when using rtfMRInf. Once such modulation is clearly established in healthy people, one can then move towards looking at specific groups vulnerable to stressful events, as as done in [Keynan and Hendler, 2017], or focus on people already suffering from stress-related disorders.

The further development of rtfMRInf with the use of more elaborately tailored feedback signals, as investigated in publication 3, can potentially improve the technique so that much more precise modulation of specific mental functions might be possible. I imagine this could help to establish neurofeedback procedures which can modulate the stress response much more precisely than what we were so far able to do.

While we were able to partially predict intervention success of an SBI using success measures of previous intervention sessions (publication 4), one can imagine much more precise predictions under integration of more available data when delivering interventions via mobile devices. The combination of SBIs with neurofeedback approaches could also be fruitful, for example one could imagine starting an intervention with neurofeedback sessions and then prolonging the effects of this training with SBIs at home, in-between and after these sessions. A further interesting field of research might focus on how such interventions are designed to help best support the patients: Applications to help people (especially children) struggling with specific mental disorders, can also take more

entertaining forms and differentiate themselves by doing so more clearly from traditional therapeutic settings, even though the underlying treatments are based on the same theories and research. An example for this are *serious games*, a rapidly growing promising field with applications for mental health [Fovet et al., 2017, Fleming et al., 2017, Lau et al., 2017], which for example has already been successfully applied to treat help-seeking adolescents struggling with depressive symptoms in an RCT with 187 adolescents in New Zealand [Merry et al., 2012]. In this case, it was even done in connection with EEG-based neurofeedback. Thus, it will become just as important to investigate how to best design such interventions, which means that they need to be developed for the individual purpose (e.g. targeted disorder, degree of interaction with mental health professional (traditional, minimal, none)) and patient (e.g. age group).

3.3 Conclusion

Neural plasticity allows us to change the brain on a molecular level with our thoughts and behavior throughout our whole life. In this thesis, I investigated whether volitional modulation of the stress response is possible, focusing on SBIs and rtfMRInf as methods to personalize interventions. Together with colleagues, I found an indication that healthy participants might under specific circumstances be able to influence their stress-related neural activity with the help of rtfMRInf, suggesting further potential of this approach in the prevention or treatment of stress-related disorders. We were also able to use data from previous sessions of an SBI to predict the success of future interventions, indicating that integrating various data into predictions for SBI can increase their fit to individual patient.

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Declaration by candidate

I herewith declare that I have independently carried out the PhD–thesis entitled *"Real-time fMRI Neurofeedback and Smartphone-based Interventions to Modulate Mental Functions"*. This thesis consists of original research articles that have been written in cooperation with the enlisted co-authors and have been published in peer-reviewed scientific journals or are in preparation for publication / submitted for publication. Only allowed resources were used and all references used were cited accordingly.

Date: _____

Signature: _____

Angelo Belardi