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The Use of Smartphone-Based Interventions to Improve Mental Health

Inaugural Dissertation submitted in fulfillment of the requirements for the degree of Doctor of Philosophy to the Department of Psychology of the University of Basel by

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Declaration of Authorship

I, Esther Patricia Stalujanis, hereby declare that I have contributed independently and substantially to this dissertation without any assistance from third parties who are not indicated. I have used only the resources indicated and have cited all references. Published or manuscripts submitted for publication were prepared in cooperation with coauthors and have not been submitted elsewhere for review or consideration, nor have they been published elsewhere. This dissertation includes the following three manuscripts:

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Contributions to individual publications

This cumulative dissertation encompasses the three publications listed below. All have been the joint effort of several contributors. My contributions to each publication are indicated by the numbers given with the references. Classification was done based on the CRediT Taxonomy (see http://casrai.org/credit for details). The following 14 roles of contribution are provided:

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; 14 – Writing: Review & Editing

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Contents

List of abbreviations

ACC	Rand Accuracy
AIC	Akaike's Information Criterion
AT	Awake-Tired
apps	Mobile Applications
BIT	Behavioral Intervention Technologies
CBT	Cognitive Behavioral Therapy
CEEBIT	Continuous Evaluation of Evolving Behavioral Intervention Technologies
CEQ	Credibility and Expectancy Questionnaire
CI	Confidence Interval
CN	Calm-Nervous
Combined	Combined Expectancy Condition
Control	Control Condition
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	Coronavirus Disease 2019
DALY	Disability-Adjusted Life-years
EDI	Edinburgh Handedness Inventory
eHealth	Electronic Health
GB	Good-Bad
GLMM	Generalized Linear Mixed-Effect Models
IAPS	International Affective Picture System
IQR	Interquartile Range
ISCED	International Standard Classification for Education
max	Maximum

MCC	Matthew's Correlation Coefficient
MDBF	Multidimensionaler Befindlichkeitsfragebogen
MDMQ	Multidimensional Mood State Questionnaire
mHealth	Mobile Health
min	Minimum
ML	Machine Learning
n obs.	Number of Observations
PE	Prospective Expectancy
PPV	Positive Predictive Value
Prospective	Prospective Expectancy Only Condition
PSS-10	Perceived Stress Scale, 10-Items Version
PTSD	Posttraumatic Stress Disorder
Retrospective	Retrospective Expectancy Only Condition
RCT	Randomized Controlled Trial
RE	Retrospective Expectancy
RF	Random Forest
RT-fMRI NF	Real-Time Functional Magnetic Resonance Imaging Neurofeedback
SAM	Self-Assessment Manikin
SD	Standard Deviation
STAI-6	Short Form of the Spielberger State-Trait Anxiety Inventory
time	Intervention Day
VAS	Visual Analog Scale
WHO	World Health Organization
YLD	Years Lived with Disability

Abstract

Mental disorders are highly prevalent and cause a high burden of disease. Even though effective treatment approaches exist, there is a large treatment gap and a substantial proportion of non-responders to traditional face-to-face psychotherapy. New treatment approaches are required. The Grand Challenges in Global Mental Health initiative called for the development of mobile and IT technologies to increase access to evidence-based care. Internet-based psychotherapeutic interventions have been found efficacious. Smartphones are widespread, ensure high availability of their users, and are equipped with technologically rich sensors. In the context of electronic Health (eHealth) and mobile Health (mHealth), the potential of smartphone-based interventions has been recognized. Due to the relative novelty and interdisciplinarity of the field, several open research questions remain. This dissertation focuses on three selected research questions on how smartphone-based interventions can be used to improve mental health. The first publication provides evidence of the applicability of smartphone-based psychotherapeutic micro-interventions evoking mood changes in a real-world setting in a non-clinical sample ($N = 27$; n obs. = 335 micro-intervention sessions) across 13 days; data was collected in a larger randomized trial. Based on data from the same study, in the second publication, evidence is provided for the utility of a machine learning-based random forest (RF) algorithm for the prediction of smartphone-based psychotherapeutic micro-intervention success regarding mood amelioration, based on contextual information. In publication 3, based on data from healthy participants in a randomized controlled trial ($N = 132$), we explored whether efficacy expectancies could be successfully induced in a smartphone-based placebo mental health intervention lasting 20 days, in the context of digital placebo effects. These findings may pave the way for future endeavors to provide personalized digital mental health interventions and to further promote the promising field of eHealth and mHealth, in line with the precision medicine approach.

Zusammenfassung

Psychische Störungen sind weit verbreitet und verursachen eine hohe globale Krankheitslast. Obwohl wirksame Behandlungsansätze existieren, bekommen viele Betroffene nicht die erforderliche Behandlung oder sprechen auf Psychotherapie im klassischen Setting (Face-to-Face) nicht an. Neue Behandlungsansätze sind deshalb erforderlich. Die «Grand Challenges in Global Mental Health»-Initiative sprach sich für die Weiterentwicklung von mobilen und Internet-basierten Technologien aus, um den Zugang zu evidenzbasierten Behandlungen zu verbessern. Die Wirksamkeit von Internet-basierter Psychotherapie konnte bereits bestätigt werden. Smartphones sind weit verbreitet, gewährleisten eine hohe Erreichbarkeit ihrer Benutzer und sind mit einer Vielzahl von technologisch komplexen Sensoren ausgestattet. Im Kontext von «Electronic Health» (eHealth) und «Mobile Health» (mHealth) wurde das Potenzial von Smartphone-basierten Interventionen bereits erkannt. Aufgrund der verhältnismässigen Neuartigkeit und Interdisziplinarität dieser Forschungsfelder bestehen jedoch noch viele offene Fragen. Die vorliegende Dissertation fokussiert auf drei ausgewählte Forschungsfragen, wie die psychische Gesundheit mithilfe von Smartphone-basierten Interventionen verbessert werden kann. Die erste Publikation liefert anhand von Daten aus einer grösseren randomisierten Studie Hinweise darauf, dass Smartphones geeignet sind, mittels psychotherapeutischer Micro-Interventionen Stimmungsveränderungen in einem Real-World-Setting in einer nichtklinischen Stichprobe (N = 27; Anzahl Beobachtungen = 335 Micro-Interventions-Einheiten) hervorzurufen. Anhand von Daten aus derselben Studie liefert Publikation 2 Hinweise darauf, dass mithilfe eines auf Maschinenlernen-basierenden Random Forest-Algorithmus anhand von kontextbezogenen Informationen der Erfolg von Smartphone-basierten Micro-Interventionen bezogen auf Stimmungsveränderungen vorhergesagt werden kann. Publikation 3 basiert auf Daten aus einer weiteren randomisiert-kontrollierten Studie (N = 132). Im Kontext des digitalen Placeboeffekts wurde untersucht,

ob in einer 20-tägigen Smartphone basierten Placebo-Intervention zur Steigerung des psychischen Wohlbefindens unterschiedliche Wirksamkeitserwartungen erzeugt werden konnten. Die Befunde ebnen den Weg für künftige Bemühungen zur Bereitstellung von digitalen Interventionen zur Verbesserung der psychischen Gesundheit und zur Weiterentwicklung der vielversprechenden Bereiche eHealth und mHealth, im Rahmen der personalisierten Medizin.

Introduction

Prevalence and burden of mental disorders

Mental disorders are highly prevalent across the globe. According to a previous meta-analysis, almost one in five persons (17.6%) met criteria for a common mental disorder during the previous 12 months, and 29.2% met lifetime prevalence (Steel et al., 2014). Mental disorders substantially affect the lives of individuals and contribute to the global burden of disease, accounting for 32.4% of years lived with disability (YLD) and 13.0% of disability-adjusted life-years (DALYs; Vigo, Thornicroft, & Atun, 2016). With estimated global direct and indirect costs at US$2.5 trillion in 2010, mental disorders cause higher economic costs than chronic somatic diseases such as cancer or diabetes (Trautmann, Rehm, & Wittchen, 2016). Among mental disorders, depressive and anxiety disorders are the most common (World Health Organization, 2017). The Global Burden of Disease Study 2010 found that depressive disorders accounted for 40.5% and anxiety disorders for 14.6% of DALYs totally caused by mental and substance use disorders (Whiteford et al., 2013).

Need for new treatment approaches

Although effective treatments exist, a substantial proportion of persons with mental disorders does not receive adequate treatment, resulting in a considerable treatment gap, defined as the percentage of persons who require mental health care but do not receive it (Kohn, Saxena, Levav, & Saraceno, 2004). It has been estimated that the treatment gap exceeded 50% worldwide and even 90% in countries with the lowest amount of economic resources (Patel et al., 2010). To address this issue, in 2011, the Grand Challenges in Global Mental Health initiative identified research priorities for the forthcoming decade, one of which involved the development of mobile and IT technologies to increase access to evidence-based care (P. Y. Collins et al., 2011). Furthermore, there is a substantial proportion of non-responders to traditional face-to-face psychotherapy (Lambert & Ogles, 2004). In this regard, Kazdin & Blase (2011) called to “reboot psychotherapy research and practice” implementing new treatment approaches, including the use of new technologies.

Internet-based psychotherapy

Internet-based respectively blended face-to-face and internet-based psychotherapeutic interventions have received considerable attention in the past ten years. They have been found efficacious, delivering comparable outcomes as conventional face-to-face psychotherapy, for instance, for the treatment of depression (Ahern, Kinsella, & Semkovska, 2018; Erbe, Eichert, Riper, & Ebert, 2017), Posttraumatic Stress Disorder (PTSD; Lewis, Roberts, Bethell, Robertson, & Bisson, 2018), anxiety disorders (Erbe et al., 2017; Olthuis, Watt, Bailey, Hayden, & Stewart, 2016), and substance abuse (Erbe et al., 2017). In contrast to many clinicians’ concern that the therapeutic alliance may only be established in a face-to-face setting, Berger and colleagues (2017) found that ratings of therapeutic alliance were roughly equivalent in internet-based psychotherapeutic interventions, as compared to conventional face-to-face psychotherapy.

Smartphone-based psychotherapeutic interventions

By the end of 2020, the number of smartphone users is expected to reach 3.5 billion worldwide and to continually increase in the coming years (Statista, 2019), particularly in emerging countries such as Brazil or South Africa where almost every second adult already owned a smartphone in 2018 (Pew Research Center, 2019). Mobile phones have evolved from simple communication tools to technologically rich and complex multi-functional companions in daily life, which are almost constantly “on”, and to which their users feel emotionally attached (Fullwood, Quinn, Kaye, & Redding, 2017). Built-in or external sensors offer the possibility to collect and measure physiological and behavioral data in the daily life of their users, such as data on location, activity, movement intensity, phone usage, bedtime/waketime, in-phone communication, or heartrate variability and cortisol level (Mohr, Zhang, & Schueller, 2017; Peng, Zhou, Lin, & Zhang, 2015; Zangheri et al., 2015). These features of smartphones make them ideal for the delivery of mental health information and psychotherapeutic techniques. Numerous health-related smartphone apps have been developed for the prevention and treatment of mental disorders, particularly for depressive and anxiety disorders (Buntrock et al., 2016; Huguet et al., 2016; Sucala et al., 2017; Torok et al., 2020). Recent meta-analyses of randomized controlled trials (RCTs) found small to moderate effect sizes, indicating that the delivery of psychotherapeutic interventions with smartphone-based devices may be an efficacious approach (Firth, Torous, Nicholas, Carney, Pratap, et al., 2017; Firth, Torous, Nicholas, Carney, Rosenbaum, et al., 2017; Marciniak et al., 2020).

Promising opportunities and challenges of digital mental health research

Electronic health (eHealth) and mobile health (mHealth) may provide promising new opportunities for personalized treatment, in line with the “precision medicine approach”. This approach aims to deliver the right treatment to the right patient at the right time (F. S. Collins & Varmus, 2015). First efforts in this field targeted at customizing drugs to individual genomic profiles of, for instance, patients with cancer (Jackson & Chester, 2015). In a next step, also non-pharmacological approaches such as psychotherapeutic treatments were tailored to a patient’s individual molecular profile (Eley et al., 2012). Recently, efforts have been made to tailor treatments based on brain signatures (Kim, Yoo, Tegethoff, Meinlschmidt, & Lee, 2015) and contextual information (van Os, Delespaul, Wigman, Myin-Germeys, & Wichers, 2013).

The fields of eHealth and mHealth are rapidly growing, deliver promising new opportunities and have gained momentum during the Coronavirus disease 2019 (COVID-19) pandemic and the associated implementation of social distancing measures (Wind, Rijkeboer, Andersson, & Riper, 2020). The novelty and interdisciplinarity of these fields encompass a broad range of open research questions. This cumulative dissertation addresses three selected topics of these emerging fields.

Evaluation of core components of digital mental health interventions to overcome the gap between technology development, research, and clinical implementation.

The efficacy of digital mental health interventions is investigated in classical RCTs, the gold standard in psychotherapy research. RCTs may take seven years or longer from grant application to the publication of results. This period covers, based on an exemplary RCT published in 2012, missed consumer technology advance from Wii (2006) over iPhone (2007) and iPad (2010) to Siri/4S (2011), indicating that the technology on which the RCT had been based was already obsolete at the time of publication (Riley, Glasgow, Etheredge, & Abernethy, 2013). Therefore, new frameworks and refinement of mobile mental health research are required (Bakker, Kazantzis, Rickwood, & Rickard, 2016; Kumar et al., 2013; Mohr, Burns, Schueller, Clarke, & Klinkman, 2013; Riley et al., 2013). In a classical RCT, well-circumscribed interventions, usually documented in therapy manuals, are evaluated. Modifications of an intervention require validation in a new RCT. A potential solution to this problem is to focus on the evaluation of core psychotherapeutic components, which can later be assembled into a full customized intervention. Therefore, it has been claimed to conduct studies in which the efficacy of specific components, features, and principles of smartphone-based interventions is investigated (Bakker et al., 2016; Mohr et al., 2015). Such specific components may be so-called “micro-interventions”. Micro-interventions are short, specific, and highly focused psychotherapeutic interventions (Baumel, Fleming, & Schueller, 2020). To date, there are only few studies in which micro-interventions were delivered to participants, mostly via online platforms (Bunge, Beard, Stephens, Leykin, & Muñoz, 2017; Bunge, Williamson, Cano, Leykin, & Muñoz, 2016; Elefant, Contreras, Muñoz, Bunge, & Leykin, 2017), one via online platform or smartphone app (Fuller-Tyszkiewicz et al., 2019). Most of the latter mentioned studies (except Fuller-Tyszkiewicz et al. (2019)) included mood changes as outcome measure. Mood represents an important clinical outcome in psychotherapeutic interventions because impairment in mood represents a key symptom in most mental disorders, particularly in mood and anxiety disorders (American Psychiatric Association, 2013), and, thus, has been a central target of Cognitive Behavioral Therapy (CBT)-based interventions for prevention and treatment of depressive and anxiety disorders (Bakker et al., 2016). As yet, there has not been a study investigating the applicability of smartphone-based psychotherapeutic micro-interventions and related changes in mood in a non-clinical sample. This research question was addressed in the first publication of this dissertation.

Application of new computational approaches for the prediction of treatment response of smartphone-based mental health interventions.

Another limitation of RCTs in psychotherapy research is that the efficacy of psychotherapeutic interventions is evaluated on average levels across groups of subjects (Bzdok & Meyer-Lindenberg, 2018; Kessler, Bossarte, Luedtke, Zaslavsky, & Zubizarreta, 2019; Rutledge, Chekroud, & Huys, 2019). This approach does not cater to the complexity of individual patients, leading to the central research question in psychotherapy research of what works for whom (Norcross & Wampold, 2011). To tailor treatments to individuals, in line with the precision medicine approach, treatment response should be predicted at the subject level. This can be accomplished with the use of new computational approaches such as machine learning (ML). ML approaches are able to identify patterns of interaction among variables in large data sets from various sources (Passos, Mwangi, & Kapczinski, 2016).

The application of ML in the field of mental health evolved from detection/classification and diagnosis of mental disorders to the prediction of treatment response, representing an important clinical outcome in psychotherapy research (Aafjes-van Doorn, Kamsteeg, Bate, & Aafjes, 2020; Lee et al., 2018; Shatte, Hutchinson, & Teague, 2019; Whiteford et al., 2013). First studies in this field used patient data or neural information for differential therapy indication of pharmacotherapy and/or psychotherapy (Chekroud et al., 2016; Costafreda, Khanna, Mourao-Miranda, & Fu, 2009; Hoogendoorn, Berger, Schulz, Stolz, & Szolovits, 2016; Lueken et al., 2016). As yet, only few studies used data of mobile/wearable sensors in the context of prognosis, treatment, and support of mental health conditions such as dementia, depression, stress, substance abuse, and wellbeing (Banos et al., 2016; Burns et al., 2011; DeMasi & Recht, 2017; Fook et al., 2009; Harikumar et al., 2016; Paredes et al., 2014; Wahle, Kowatsch, Fleisch, Rufer, & Weidt, 2016). However, none of these studies investigated the applicability of ML for the prediction of treatment response to preventive smartphone-based mental health interventions. This research question was addressed in the second publication of this dissertation.

Scrutinizing digital placebo effects as a potential mechanism of action of smartphone-based mental health interventions.

As above-mentioned, there is evidence of the efficacy and effectiveness of smartphone-based interventions, for instance, for the prevention and treatment of depressive or anxiety disorders (Firth, Torous, Nicholas, Carney, Pratap, et al., 2017; Firth, Torous, Nicholas, Carney, Rosenbaum, et al., 2017). Potential mechanisms of action remain unclear. Torous and Firth

(2016) introduced the concept of digital placebo effects and suggested placebo-like effects may be an underlying mechanism of action of mobile health interventions. Traditionally, placebos play an important role as control condition in blinded RCTs and should be minimized to enable a valid investigation of the efficacy of a drug or a medical treatment procedure (Enck, Bingel, Schedlowski, & Rief, 2013).

Outcome expectancies have been suggested as a potential factor of how placebos work, that means, the belief that a potential drug or intervention may work may produce an effect (Petrie & Rief, 2019). Positive associations between favorable outcome expectancies and desirable therapeutic effects have been found for a wide range of medical and mental conditions (Keefe et al., 2017; Peerdeman et al., 2016; Rutherford, Wager, & Roose, 2010; Wilhelm, Winkler, Rief, & Doering, 2016). In this regard, it has been suggested to maximize placebo effects in some contexts by enhancing patient's expectations to improve treatment outcomes (Enck et al., 2013; Keefe et al., 2017). Particularly mobile apps deliver promising opportunities and advantages to provide and investigate highly standardized expectancy interventions in a blinded manner (Gruszka, Burger, & Jensen, 2019). There are only few studies addressing digital placebo effects. The few available are conceptional (Torous & Firth, 2016), focused on methodological recommendations for smartphone-based RCTs (Gruszka et al., 2019; Tonning, Kessing, Bardram, & Faurholt-Jepsen, 2019) or used a sham version of an active app intervention as control condition (Krzystanek, Borkowski, Skalacka, & Krysta, 2019). As yet, there has not been a study investigating efficacy expectancies in the context of digital placebo effects in a placebo smartphone-based mental health intervention. This research question was addressed in the third publication of this dissertation.

Research questions addressed in this dissertation

In sum, to adequately address the grand challenge in mental health on the development of mobile and IT technologies to increase access to evidence-based care (P. Y. Collins et al., 2011), there is a need to i) evaluate core components of digital mental health interventions to overcome the gap between technology development, research, and clinical implementation, ii) further scrutinize the utilization of new computational approaches for the prediction of treatment response of smartphone-based mental health interventions, and iii) explore digital placebo effects as potential mechanisms of action of smartphone-based mental health interventions.

In this context, the aim of this dissertation was to further scrutinize the utilization of smartphone-based interventions to improve mental health. The three publications included are based on data from two studies. Publications 1 and 2 are based on data from 27 healthy participants who participated in a larger neurofeedback trial. Publication 3 is based on data from an RCT, conducted with 132 healthy participants.

Specifically, in the first publication of this dissertation, *"Smartphone-Based Psychotherapeutic Micro-Interventions to Improve Mood in a Real-World Setting"*, the use of ambulatory smartphone-based micro-interventions based on psychotherapeutic techniques to evoke mood changes was explored in a real-world setting.

In the second publication, *"Personalized prediction of smartphone-based psychotherapeutic micro-intervention success using machine learning"*, the utility of an ML-based random forest (RF) algorithm for the prediction of smartphone-based psychotherapeutic micro-intervention success in evoking mood changes, based on contextual information, was explored.

In the third publication, *"Induction of Efficacy Expectancies in an Ambulatory Smartphone-based Digital Placebo Mental Health Intervention: Randomized Controlled*

Trial", it was investigated whether efficacy expectancies could be successfully induced in an ambulatory smartphone-based placebo mental health intervention.

Original research papers

Publication 1: Smartphone-Based Psychotherapeutic Micro-Interventions to Improve Mood in a Real-World Setting

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Smartphone-Based Psychotherapeutic Micro-Interventions to Improve Mood in a Real-World Setting

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Background: Using mobile communication technology as new personalized approach to treat mental disorders or to more generally improve quality of life is highly promising. Knowledge about intervention components that target key psychopathological processes in terms of transdiagnostic psychotherapy approaches is urgently needed. We explored the use of smartphone-based micro-interventions based on psychotherapeutic techniques, guided by short video-clips, to elicit mood changes.

Method: As part of a larger neurofeedback study, all subjects—after being randomly assigned to an experimental or control neurofeedback condition—underwent daily smartphone-based micro-interventions for 13 consecutive days. They were free to choose out of provided techniques, including viscerosensory attention, emotional imagery, facial expression, and contemplative repetition. Changes in mood were assessed in real world using the Multidimensional Mood State Questionnaire (scales: good–bad, GB; awake–tired, AT; and calm–nervous, CN).

Results: Twenty-seven men participated on at least 11 days and were thus included in the analyses. Altogether, they underwent 335, generally well-tolerated, micro-intervention sessions, with viscerosensory attention (178 sessions, 53.13%) and contemplative repetition (68 sessions, 20.30%) being the most frequently applied techniques. Mixed models indicated that subjects showed better mood [GB: $b = 0.464$, 95%confidence interval (CI) [0.068, 0.860], $t_{(613.3)} = 2.298$, $p = 0.022$] and became more awake [AT: $b = 0.514$, 95%CI [0.103, 0.925], $t_{(612.4)} = 2.456$, $p = 0.014$] and calmer [CN: $b = 0.685$, 95%CI [0.360, 1.010], $t_{(612.3)} = 4.137$, $p < 0.001$] from pre- to post-micro-intervention. These mood improvements from pre- to post-micro-intervention were associated with changes in mood from the 1st day until the last day with regard to GB mood ($r = 0.614$, 95%CI [0.297, 0.809], $p < 0.001$), but not AT mood ($r = 0.279$, 95%CI [−0.122, 0.602], $p = 0.167$) and CN mood ($r = 0.277$, 95%CI [0.124, 0.601], $p = 0.170$).

Discussion: Our findings provide evidence for the applicability of smartphone-based micro-interventions eliciting short-term mood changes, based on techniques used in psychotherapeutic approaches, such as mindfulness-based psychotherapy, transcendental meditation, and other contemplative therapies. The results encourage exploring these techniques' capability to improve mood in randomized controlled studies and patients. Smartphone-based micro-interventions are promising to modify mood in real-world settings, complementing other psychotherapeutic interventions, in line with the precision medicine approach. The here presented data were collected within a randomized trial, registered at ClinicalTrials.gov (Identifier: NCT01921088) https://clinicaltrials.gov/ct2/show/NCT01921088.

Keywords: behavioral intervention technology, ehealth, health information technology, information and communication technology, Internet- and mobile-based intervention, mental disorder, mhealth, wireless health

INTRODUCTION

Mental disorders are one of the leading global causes of disability (Murray et al., 2012). Besides the personal suffering, their direct and indirect economic costs are tremendous (Wittchen et al., 2011; Olesen et al., 2012). A prominent consortium of researchers, advocates, and clinicians identified key "grand challenges in global mental health" in terms of major research priorities for improving the lives of people with mental illnesses around the world (Collins et al., 2011). Notably, one of the prioritized goals is to improve treatments and expand access to mental health care, with the development of mobile and Internet technologies to increase access to evidence-based care being among the top challenges (Collins et al., 2011). This need is underscored by the fact that in countries, regardless of their economic status, the demand for individual face-to-face psychotherapy is already exceeding or will exceed mental health service supply in the future (Kazdin and Blase, 2011). Therefore, new forms of treatment are required that can complement or expand our current approaches in treating people who suffer from mental disorders (Kazdin and Blase, 2011; Kostkova, 2015).

To this end, Internet-based psychotherapies have received considerable attention during the past decade, lowering the barrier to access mental health service. Most studies indicated that Internet-delivered interventions were efficacious in achieving positive behavioral change or symptom reduction, with no clear evidence of superiority or inferiority as compared to face-to-face interventions (Cuijpers et al., 2010; Griffiths et al., 2010; Richards and Richardson, 2012; Andersson et al., 2014; Riper et al., 2014; Ebert et al., 2015; Richards et al., 2015; Kuester et al., 2016; Melioli et al., 2016; Olthuis et al., 2016; Zachariae et al., 2016).

The advent of mobile information technologies has taken this low-barrier approach to the next level. In the year 2020, 70% of the world's population will use a smartphone (Ericsson, 2015). The core features of smartphones and other mobile devices are that they are running most of the time, are used in a variety of situations during daily life, and ensure a broad reachability of their users beyond calls, e-mails, short messaging, or instant messaging. Unlike the dissemination of many other technologies, the rapid uptake of mobile phones has not been restricted to developed countries (Kay et al., 2011). Furthermore, mobile phones are the preferred means of communication among young people, the age group most unlikely to seek treatment (Oliver et al., 2005). However, some target populations, such as veterans, that experience mental health service gaps may also be more difficult to reach via smartphone-based interventions, as compared to the general population (Klee et al., 2016). Smartphones are increasingly complex, computationally powerful, sensory-rich, and integrated with social networking (Morris and Aguilera, 2012). These factors make them ideal for the delivery of mental health information, digital psychotherapeutic techniques and support anywhere, in real-time and when needed, the latter identified amongst others using sensors integrated in the smartphone (McClernon and Roy Choudhury, 2013). This is in line with the "precision medicine approach," aiming to provide the right treatment, at the right time, and for the right person (Insel, 2014; Collins and Varmus, 2015). Integrating smartphones in mental healthcare provides a wealth of opportunities, including to overcome the innovation gap by allowing for "disruptive innovation" (Bower and Christensen, 1995), and to provide the basis for new, personalized forms of treatment (Ehrenreich et al., 2011; Zeevi et al., 2015).

Modifying mood or inducing certain mood states in the laboratory, using different approaches in non-clinical samples, has a long-standing history in psychological research (Velten, 1968; Martin, 1990; Schaefer et al., 2010). However, there are only few studies that examined the use of exclusively smartphone-based interventions to modify mood or affective states in healthy populations (e.g., Cipresso et al., 2012); which is in contrast to the large number of studies using smartphones for mood assessment (e.g., Asselbergs et al., 2016). However, a better understanding on how smartphones may be used to modify mood in healthy subjects may provide an important basis for its future application in clinical samples.

Notably, even though an increasing number of mobile applications (apps) that claim to target mental health are available in software repositories (Mani et al., 2015; Nicholas et al., 2015; Shen et al., 2015), as yet, studies that evaluate the effects of applying smartphones as a means of behavior modification are relatively scarce (Donker et al., 2013; Mohr et al., 2013a; Harrison and Goozee, 2014; Mani et al., 2015; Olff, 2015; Torous and Powell, 2015; Bakker et al., 2016). Initial studies provide evidence that smartphone-based interventions have the potential to reduce symptoms of mental disorders, such as anxiety, depression, schizophrenia, and substance use disorders (Watts et al., 2013; Ben-Zeev et al., 2014; Gustafson et al., 2014; Ly et al., 2014; Ahmedani et al., 2015). Further, there is first evidence that mobile technology, including smartphone-based applications, can boost the efficacy of psychotherapy and behavioral interventions (Lindhiem et al., 2015). In sum, further research on smartphone-based interventions in non-clinical samples is highly warranted, and may provide an important basis for future studies and applications, aiming at improving and facilitating prevention and treatment of mental disorders, which has the potential to complement established treatment approaches, serving great clinical and societal relevance.

One particular challenge in the field of mobile mental health research is the mismatch of the paces of research and technology development, with rather long timeframes of classical randomized controlled trials (RCTs), the gold standard of research designs to determine the efficacy of an intervention, with a median duration of more than 5 years from initial enrollment to publication and much longer timeframes until implementation into routine care (Ioannidis, 1998; Riley et al., 2013; Clough and Casey, 2015). This has led to the call for new frameworks and refinement of mobile mental health research (Kumar et al., 2013; Riley et al., 2013; Mohr et al., 2013a,b; Ben-Zeev et al., 2015; Clough and Casey, 2015; Nicholas et al., 2015; Bakker et al., 2016). Classical RCTs evaluate a well-circumscribed intervention; hence modifications of the intervention require conducting a new RCT. One solution to this problem, we believe, is to evaluate core psychotherapeutic components and key features of interventions, which can then guide the assembly of the intervention as a whole, if desired still followed by an RCT. To this end, studies that focus on the evaluation of important elements, characteristics, and principles of smartphone-based interventions, starting with non-clinical samples and later being applied to patients, may be of great importance (Mohr et al., 2014; Alkhaldi et al., 2016; Bakker et al., 2016).

The idea to focus on core intervention components is in line with transdiagnostic treatment approaches, which center on core disease mechanisms to improve the understanding and treatment of mental disorders (Wilamowska et al., 2010; Thompson-Hollands et al., 2014; Newby et al., 2015, 2016). One central target of psychotherapeutic interventions is the improvement of mood, with mood disturbances being the key symptom of a variety of mental disorders (American Psychiatric Association, 2013). Furthermore, mood plays a key role in the quality of daily life, and influences personal and social adjustment and physical health, social interactions, and problem solving (Fredrickson, 2004; Shallcross et al., 2010). Hence, the advancement of easily applicable interventions to improve mood is of paramount importance.

Our goal was to explore in a real-world setting, in a non-clinical sample, the use of smartphone-based micro-interventions and related changes in mood. We thereby applied micro-interventions in form of psychotherapeutic techniques that have already been used as components of face-to-face psychotherapy (see Paredes et al., 2014), guided by short video-clips of <5 min duration. More specifically, we aimed at estimating changes in mood and hypothesized that mood would improve from pre- to post-micro-intervention. Furthermore, we evaluated whether these changes were related to changes in mood from the first to the last micro-intervention day, and finally, whether they varied over time and between techniques. The analyzed data were collected from 13 daily micro-intervention sessions, as part of a larger neurofeedback study, in which two real-time functional magnetic resonance imaging neurofeedback (RT-fMRI NF) sessions were conducted, one before all daily micro-intervention sessions and one after, separated by 14 days.

MATERIALS AND METHODS

Outline of the Study Procedure

Overall Study Procedure

The data presented here were collected within a randomized trial, registered at ClinicalTrials.gov (Identifier: NCT01921088) https://clinicaltrials.gov/ct2/show/NCT01921088. The aim of this larger study was to assess the application of real-time functional magnetic resonance imaging neurofeedback (RT-fMRI NF) to modulate the response to an acute stressor in form of the Stroop color word interference task. RT-fMRI NF is a type of self-regulation technique that provides an individual with feedback about specific brain activity using functional magnetic resonance imaging in connection with a related behavior; The underlying assumption at the core of this practice is that through RT-fMRI NF a subject can learn to regulate neural activity and related mental functions (see Thibault et al., 2016).

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_004095].

The whole study consisted of three laboratory visits and 13 days of ambulatory smartphone-based micro-interventions using psychotherapeutic strategies, the latter following the second laboratory visit on which the RT-fMRI NF procedure was applied for the first time (see **Figure 1**; for a brief overview of the whole study, please refer to Supplementary Material Data Sheet 1). The data presented here were collected during the preliminary testing day and the smartphone-based micro-interventions, with the exception of the feedback on the micro-interventions that was collected before the RT-fMRI NF procedure on experiment day 2. First, we screened subjects interested in study participation during a telephone interview for any history of neurological or mental disorders and invited those eligible to a laboratory visit, the preliminary testing day, on which we verified whether subjects met all eligibility

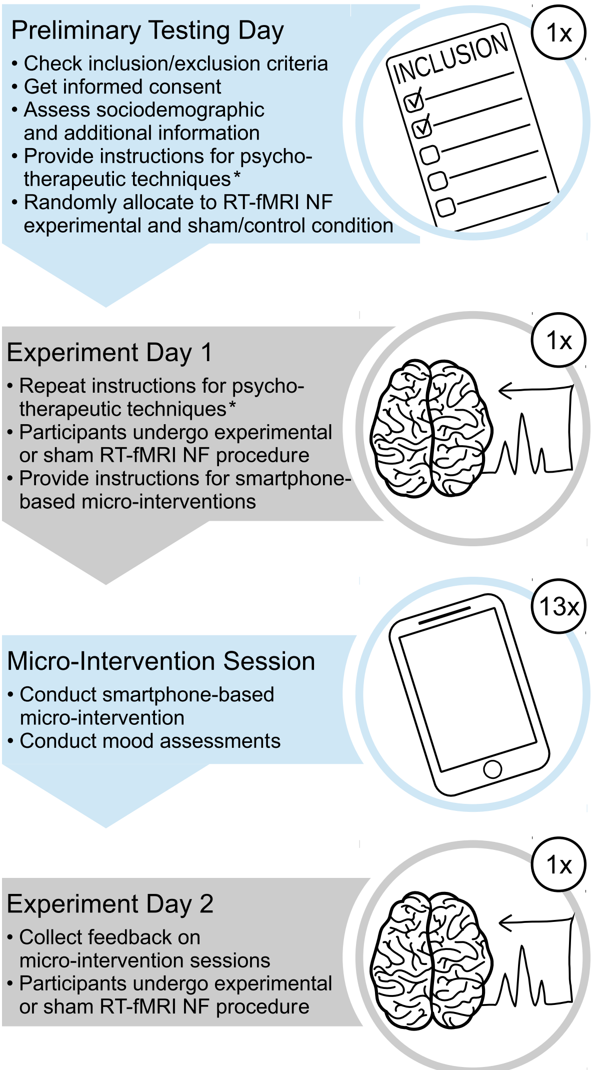

FIGURE 1 | Outline of the larger study. The data presented here were collected during the preliminary testing day and the smartphone-based micro-interventions, with the exception of the feedback on the micro-interventions that was collected before the RT-fMRI NF procedure on experiment day 2. *We instructed participants in four psychotherapeutic techniques, first at the preliminary testing day, then at the beginning of the session at experiment day 1, and briefly reiterated these instructions at the end of this session; RT-fMRI NF, real-time functional magnetic resonance imaging neurofeedback.

criteria (see below). Subjects fulfilling eligibility criteria and interested in study participation were asked to provide additional data via questionnaires, were instructed in psychotherapeutic techniques (see section below) to be practiced in different phases of the study, and invited to two further laboratory visits (14 days apart from each other) for a RT-fMRI NF experiment. Between these two experiment days, subjects participated in smartphone-based micro-interventions, during which they practiced the psychotherapeutic techniques they had previously learned on the preliminary testing day and experiment day 1, respectively.

Preliminary Testing Day

At the preliminary testing day, we first outlined the whole study procedure to the subjects and collected their written informed consent. Then, we had them practice four psychotherapeutic techniques (for details, see below), which they later applied during the RT-fMRI NF experiment and the micro-interventions. In this first introduction to the techniques, we used detailed instructions and handed out copies with the written instructions to the participants, so that they could follow the text while we explained the techniques. Next, we explained them all other tasks relevant for the RT-fMRI NF experiment procedure (details available from the authors on request). We then asked the participants to fill in a set of questionnaires and checklists to verify their eligibility to the experiment and gather additional information (e.g., sociodemographic data). A detailed description of those questionnaires relevant for this publication is given below. The experimenter then looked through the results and decided upon inclusion of participants. In case of inclusion, the experimenter and subject made an appointment for the next visit at the laboratory for experiment day 1 (6 weeks later at maximum).

Psychotherapeutic Techniques

We instructed the participants in four psychotherapeutic techniques, first at the preliminary testing day, then at the beginning of the session at experiment day 1, and briefly reiterated these instructions at the end of this session. We told the participants that they might find these techniques useful to accomplish the upcoming tasks during the RT-fMRI NF experiment in terms of modulating their brain activity as well as their stress level. The following four techniques were instructed: (i) viscerosensory attention, (ii) emotional imagery, (iii) facial expression, and (iv) contemplative repetition. Additionally, participants were allowed to use (v) any other individual technique that they felt would be helpful. A brief outline of the techniques, as provided at the end of experiment day 1, is depicted in **Table 1**. In brief, (i) viscerosensory attention consisted of shifting attention toward vs. away from bodily sensations, for example heartbeat or breathing; (ii) emotional imagery consisted of imagining emotionally positive (e.g., great holidays, a beloved person), negative (e.g., a stressful exam, a conflict) or neutral (e.g., a bus ride, reading the newspaper) situations; (iii) facial expression consisted of making different emotional facial expressions, e.g., a happy, angry, or neutral face; and (iv) contemplative repetition consisted of repeating a short simple sentence or word over and over again, or slowly and repeatedly counting from 1 to 10. The shifting between different extremities, as instructed for viscerosensory attention, emotional imagery, and facial expression, was to exploit a preferably large scope of modifiability. To ensure that subjects well remembered the techniques for application during the smartphone-based micro-interventions, at the end of experiment day 1, we asked subjects (i) to take some time to vividly remember the technique that they had just applied in the scanner and that worked best for them, and to briefly describe this technique in written form; (ii) to think of and write down a keyword that might help them to call up this technique once they would apply it during the

TABLE 1 | Description of techniques applied during the micro-interventions.

Technique	Instruction
Viscerosensory attention	*"Shift your attention toward vs. away from bodily sensations, for example your heartbeat, breathing, or feelings in stomach. Keep your attention focused on each sensation for a while."*
Emotional imagery	*"Imagine emotionally positive, negative, or neutral situations, and shift your attention between them. For example think of a beloved person, a stressful exam or a conflict, or a bus ride. Keep your attention focused on each situation for a while."*
Facial expression	"*Make different emotional expressions with your face and keep each for a while (e.g., happy face, angry face, neutral face)."*
Contemplative repetition	*"Repeat a short, very easy sentence, or slowly count from 1 to 10 (repeat this over and over again)."*
Other technique	*"Remember the strategy that you have successfully practiced in the scanner. Please concentrate and practice this strategy during the next minutes."*

subsequent micro-intervention sessions; and (iii) to think of a picture that might help them to recall this technique during the micro-intervention sessions, and to describe it in words or draft it. All four psychotherapeutic techniques have been shown to be related to changes in mood (Kleinke et al., 1998; Holmes et al., 2006; Lane et al., 2007; Pollatos et al., 2015), with potential for the treatment of mental disorders (Ito et al., 2001; Holmes et al., 2007; Orme-Johnson and Barnes, 2014; Lin et al., 2015).

Smartphone-Based Micro-Interventions

To familiarize the participants with the smartphone-based micro-intervention, we asked all subjects to undergo one micro-intervention session for training purposes, while still in the laboratory at the end of experiment day 1. Data collected during this training session were not included in our analyses.

On the 13 days between experiment day 1 and 2, each participant underwent one session of smartphone-based micro-intervention per day during their daily life, in which he applied one of the psychotherapeutic techniques outlined above. We instructed subjects to use their own smartphones for participating in the micro-intervention sessions (see Supplementary Material Table 1 for additional information on smartphone types, operating systems, and Internet browsers used). Subjects were free to choose the time of day at which they underwent the micro-intervention session. The time window during which the subjects had to undergo the daily micro-intervention session started each day at 0800 h when they received the invitation-e-mail including the personalized and day-specific hyperlink for access to the micro-intervention session. This hyperlink expired at 0300 h on the following day. In addition to the daily invitation-e-mail at 0800 h, subjects received a reminder-e-mail at 2000 h if they had not yet participated since the last invitation.

We used EFS Survey 10.0 (Questback GmbH, Berlin, Germany) to conduct the smartphone-based micro-interventions, including instructions, presentation of a video-clip, and collection of questionnaire data, as well as for automatically sending the invitation- and reminder-e-mails.

The detailed procedure of each session was as follows: (1) Subjects used their smartphones to connect via internet browser, using a personalized hyperlink provided in the daily invitation or reminder e-mails, to the server hosted by Questback. (2) We instructed the subjects by text display to seek a quiet place allowing them to concentrate on the micro-intervention, and to ensure having a stable Internet connection. Furthermore, we instructed them that the end of the micro-intervention would be signalized by a sound, and that they should therefore ensure to plug in their headphones or set the loudspeakers of their smartphone on high volume, if possible, and that alternatively, the end of the micro-intervention would also be recognizable by visual cues. (3) We asked the subjects to enter their individual subject ID that we had previously provided, as well as a self-generated personal code that they had already generated during the preliminary testing day. This code allowed verifying subject identity. (4) Subjects responded to the Multidimensional Mood State Questionnaire (MDMQ), described in more detail below, and the self-assessment manikin (SAM) scales (Bradley and Lang, 1994). (5) We instructed the subjects to prepare for the micro-intervention, including (i) asking them to remember the technique that they successfully applied during experiment day 1 and telling them that they should use this technique on each of the daily micro-intervention sessions, (ii) instructing them that a micro-intervention session would consist of two rounds lasting 2 min each, interrupted by a pause of 30 s and that in order to start with the session, they should click on the "play"-button of the video player; (iii) asking them—if their Internet connection was weak—to click on the "stop"-button to wait until the player had completely loaded the video, then to reset the video, and to the start the video by clicking on "play" again; and (iv) informing them that the end of the micro-intervention session was signalized by a sound and visually announced in the video, and instructing them not to click on "Continue" before they heard the sound or before the end of the video was reached, as this is important to ensure a standardized duration of the session for each participant and on each day; (v) After this, we asked subjects to select the psychotherapeutic technique they wanted to use during this session (for details, see previous sections). (6) Then, subjects underwent the micro-intervention by following the instructions provided within a short video-clip (duration each: ~4 min 40 s), presented according to the technique that they wanted to apply (the video-clips are provided as Supplementary Material Video 1–5; details of the structure and content of the video-clips are as Supplementary Material Data Sheet 2; additional information regarding the video files as Supplementary Material Data Sheet 3). (7) Subjects again responded to the MDMQ and the SAM scales. (8) Then, subjects replied to two questions related to the micro-intervention session: first, they were asked how successful their session was today, with possible replies on a 5-level scale ranging from −2 (much less than expected/very bad) to +2 (much more than expected/very good). Second, they were asked how they could optimize their micro-intervention (e.g., conditions, motivation, timing, etc.), with an open answer format. The aim of this second question was to guide subjects toward individual optimization of their personal micro-intervention. (9) The session finished by thanking them for their participation in today's session and reminding them of the next micro-intervention session on the subsequent day (or of experiment day 2 on the last day of micro-intervention sessions).

For each page that EFS provided, it recorded a time-stamp, from which we were able to derive date and time of each micro-intervention session.

Assessment Instruments

Assessment of Inclusion/Exclusion Criteria

We applied a set of well-established questionnaires (presented as paper-pencil questionnaires or electronically) to gather information from the participants along the study. Further, we used a set of short checklists to collect additional information, such as data regarding eligibility criteria and feedback regarding the smartphone-based micro-interventions.

To verify the eligibility criterion "right handedness" and the exclusion criterion "color-blindness," we asked the study participants to fill in the Edinburgh Handedness Inventory (EHI; Oldfield, 1971) and the Ishihara test for color-blindness (Ishihara and Force, 1943), respectively, on the preliminary testing day.

Assessment of Mood and Feedback on Micro-Intervention Sessions

We applied the 12-item MDMQ to assess current mood on three dimensions ranging from good to bad (GB), awake to tired (AT), and calm to nervous (CN). The MDMQ is the English version of the German *Mehrdimensionale Befindlichkeitsfragebogen* (MDBF; Steyer et al., 1997; Steyer, 2014), which is a well-established tool for the assessment of current mood, with very good psychometric properties, especially suited for repeated measures within short intervals. For each dimension, a score is calculated, ranging from 4 to 24. Depending on the dimension, high scores suggest positive affectivity, wakefulness, and calmness, respectively. We applied the MDMQ twice during each smartphone-based micro-intervention session, both before and after subjects practiced the psychotherapeutic technique.

We obtained feedback regarding the smartphone-based micro-intervention sessions at the beginning of experiment day 2, asking the subjects if they agreed with the four statements displayed in Supplementary Material Table 2. Additionally, participants were encouraged to provide further comments regarding the micro-intervention sessions.

Two researchers (AB and JA) independently entered all data from paper-pencil questionnaires into electronic spreadsheets, and a third researcher (ES) crosschecked their entries.

Participants

We recruited participants from the student body of the Korea University. Advertisements for the study were posted on the university website and a local bulletin board. Participants had to fulfill the following eligibility criteria, which were based on the requirements of the larger RT-fMRI NF study: male, age 18–65 years, right-handed, no color-blindness, no history of cardiovascular or neurological diseases or mental disorders, sufficient English language skills to follow the experimental instructions, and self-reported at least minimal familiarity with smartphone-use to carry out the micro-interventions. The sample size was determined *a priori*, based on the requirements of the randomized trial assessing RT-fMRI NF effects, to provide sufficient statistical power to test the main hypotheses of the trial. Samples size estimates were based on previous studies, demonstrating large effect sizes within RT-fMRI NF paradigms (deCharms et al., 2005; Yoo et al., 2008; Kim et al., 2015). We estimated, by calculating *a priori* power analysis (using G* Power 3, Faul et al., 2007, RRID: SCR_013726) that with $n = 14$ subjects in each condition, effects of $d = 1.0$ can be detected with sufficient power ($1–ß > 0.80$; given $\alpha = 0.05$, one-sided test).

After completion of the study, each subject received 60,000 KRW (≈57 USD) in compensation for his participation. The compensation was split in three parts, for the participation at experiment day 1, smartphone-based micro-interventions, and experiment day 2, and paid out in part if the subject did not take part in the complete study.

Statistical Analyses

We checked the data for distribution properties and verified normality by inspecting histograms and qq-plots. For descriptive analyses, we calculated means and standard deviations for continuous normally distributed variables and absolute and relative frequencies for categorical variables with categories outlined in **Table 2**.

As the values of the scales of the MDMQ were approximately normally distributed, transformation was not required. Twenty-six of the 27 participants applied the same psychotherapeutic technique across micro-intervention days, but one subject extensively varied the psychotherapeutic technique across days. Therefore, we did not enter psychotherapeutic technique as factor at the level of the micro-intervention day, but entered it at the participant level. To this end, we assigned each of the above-mentioned 26 participants to the psychotherapeutic technique category that they used, and created an additional category "mixed techniques" for the subject that extensively varied the psychotherapeutic techniques. As in four of the resulting six categories there were only few subjects ("emotional imagery", $n = 3$; "facial expression", $n = 2$; "other technique", $n = 2$; and "mixed techniques", $n = 1$), we collapsed these four categories, leading to the trichotomous variable "psychotherapeutic technique" with the three levels "viscerosensory attention" ($n = 14$), "contemplative repetition" ($n = 5$), and "other" ($n = 8$).

Each scale of the MDMQ was entered as outcome variable in separate linear mixed-effects models (Singer and Willett, 2003), to estimate mood changes from pre- to post-micro-intervention and across micro-intervention days, as well as differences in mood changes from pre- to post-micro-intervention across micro-intervention days and between psychotherapeutic

TABLE 2 | Characteristics of the study sample ($N = 27$).

Variable	Category	n	(%)*
CATEGORICAL VARIABLES			
Marital status	Single	20	(74.07%)
	In a relationship	7	(25.93%)
Highest degree	High school or equivalent	24	(88.89%)
	Bachelor's degree	3	(11.11%)
Size of household (including participant)**	1	1	(3.85%)
	2	0	(0%)
	3	1	(3.85%)
	4	22	(84.62%)
	5	2	(7.69%)
"I am very experienced in using smartphones"	Strongly agree	7	(25.93%)
	Agree	14	(51.85%)
	Neutral	4	(14.81%)
	Disagree	1	(3.70%)
	Strongly disagree	1	(3.70%)
Variable (unit)	**Mean**	**(*SD*)**	**Range [min, max]**
CONTINUOUS VARIABLES			
Age (years)	24.32	(2.27)	[19.75, 28.70]
Full time education (years)	15.15	(1.38)	[12, 18]

**Percentages may not total 100 due to rounding; **Information from one subject missing; max, maximum; min, minimum; SD, standard deviation.*

techniques. Furthermore, we adjusted analyses for the condition (experimental or sham/control condition) to which subjects had been assigned within the larger randomized controlled trial from which the data was derived. Hence, we entered the following predictors into the model: (i) "pre- vs. post-micro-intervention", (ii) "micro-intervention day" (dimensional, day 1–13), iii) "psychotherapeutic technique" (trichotomous, see above), and iv) "condition" (experimental vs. sham/control), as well as the interactions of "pre- vs. post micro-intervention" with "micro-intervention day", "psychotherapeutic technique", and "condition". We entered random intercept and random slope parameters when this improved model fit, with the latter being assessed based on Akaike's Information Criterion (AIC; Singer and Willett, 2003). Furthermore, we tested whether entering a higher order polynomial of the variable "micro-intervention day" would improve model fit. We first fitted models including main and interaction effects, as outlined above. In case of the interaction effects being statistically not significant, we repeated analyses with main effects only, leading to the main results reported. We calculated 95% confidence intervals (CIs) using the Wald method. For the main mixed model analyses, we included all subjects that took part in at least 3 micro-intervention sessions. Mixed models accommodated further missing data.

To test whether average mood improvements from pre- to post-micro-interventions were associated with overall baseline mood improvements over all intervention days, we calculated Pearson product-moment correlation coefficients between the mean of the non-missing mood changes from pre- to post-micro-interventions averaged across days 2–12 and change in mood from pre-micro-intervention day 1 to pre-micro-intervention day 13, separately for GB, AT, and CN mood.

All tests were two-tailed and we set the significance level at 0.05. We used the statistical software package R (version 3.2.3 and above; R Project for Statistical Computing, RRID: SCR_001905; R Core Team, 2015) for all data analyses and statistical testing, including the packages to conduct the mixed models, "lme4" (Bates et al., 2014) and "optimx" (Nash and Varadhan, 2011), as well as further packages, required for data preparation and descriptive statistics "car" (Fox and Weisberg, 2011), "dplyr" (Wickham and Francois, 2015), "haven" (Wickham and Miller, 2015), "Hmisc" (Frank and Dupont, 2015), "lmerTest" (Kuznetsova et al., 2015), "lsmeans" (Lenth, 2016), "pastecs" (Grosjean and Ibanez, 2014), and "tidyr" (Wickham, 2015).

RESULTS

Flow and Descriptive Information on Study Participants

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 <3 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 2**. (For the sake of transparency, characteristics of the full study sample ($N = 30$) is provided in Supplementary Material Table 3).

Descriptive Information on Smartphone-Based Micro-Intervention Sessions

The 27 subjects participated in 336 out of 351 possible smartphone-based micro-intervention sessions in total (95.73%). The mean number of micro-intervention sessions per subject was 12.44 (standard deviation, $SD = 0.80$, Range: 11–13) [respective information regarding the sample of $N = 30$ participants, who in total participated in 342 out of 390 possible micro-intervention sessions (87.69%) is provided in Supplementary Material Table 3]. 26 sessions (7.74%) were conducted at 0800 h or later but before 0900 h, 63 sessions (18.75%) were conducted at 0900 h or later but before 1200 h, 54 sessions (16.07%) were conducted at 1200 h or later but before 1500 h, 44 sessions (13.10%) were conducted at 1500 h or later but before 1800 h, 69 sessions (20.54%) were conducted at 1800 h or later but before 2100 h, 69 sessions (20.54%) were conducted at 2100 h or later but before 0000 h, and 11 sessions (3.27%) were conducted at 0000 h or later but before 0300 h. The relative frequency of psychotherapeutic techniques applied during the micro-intervention sessions is depicted in **Figure 3**.

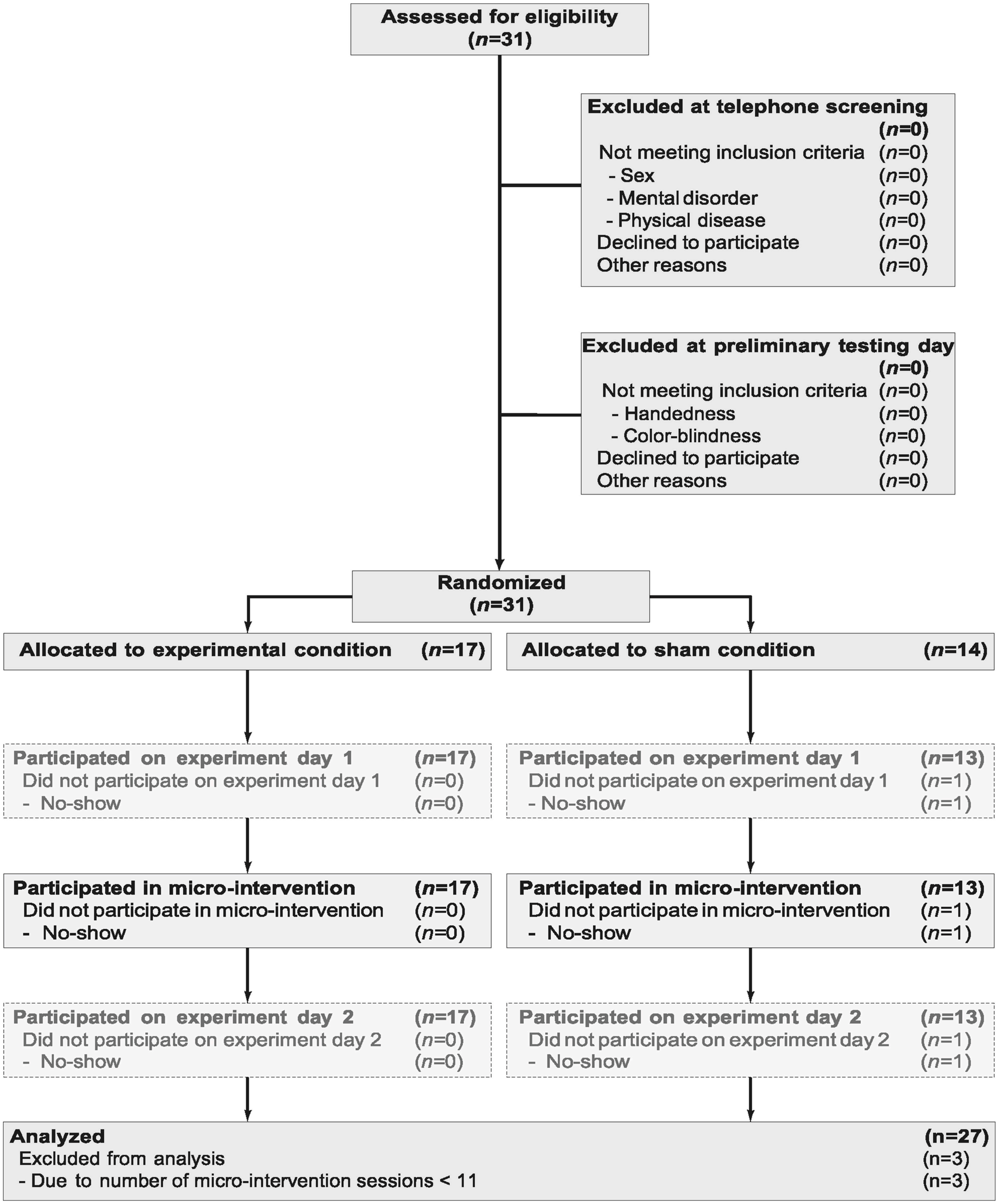

FIGURE 2 | Participant flow through study.

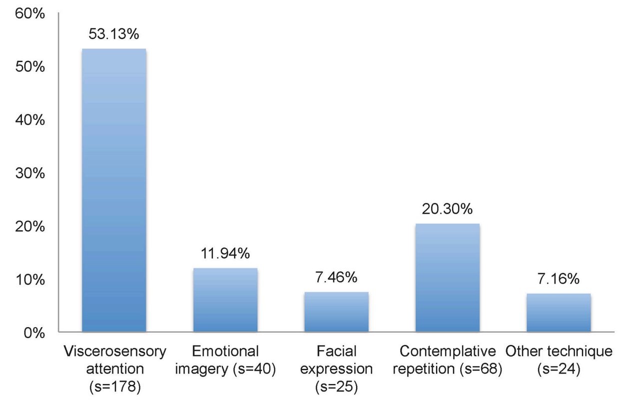

FIGURE 3 | Relative frequency of psychotherapeutic techniques applied during the smartphone-based micro-intervention sessions. Information on selected technique missing for one session; s, number of sessions.

Main Results from the Mixed Model Analyses

Changes in mood from pre- to post-micro-intervention and across micro-intervention days are depicted in **Figure 4** (MDMQ good-bad mood; **Figures 4B,A**, respectively), **Figure 5** (MDMQ awake-tired mood; **Figures 5B,A**, respectively), and **Figure 6** (MDMQ calm-nervous mood; **Figures 6B,A**, respectively). Mood changes stratified according to psychotherapeutic technique are depicted in **Figure 7**. All mixed models included a random intercept and slope of day varying among subjects. Entering "micro-intervention day" as higher order than linear polynomial did not improve model fit. In all three mixed models (with GB, AT, and CN as outcome) none of the interaction terms were statistically significant (see Supplementary Material Table 4 for related statistical parameters) and they were hence removed from the models. This means that there was no indication that changes in mood from pre- to post-micro-intervention differed across micro-intervention days, between psychotherapeutic techniques, and between conditions.

With regard to good or bad mood as outcome, mood improved from pre- to post-micro-intervention [$b = 0.464$, 95%CI [0.068, 0.860], $t_{(613.3)} = 2.298$, $p = 0.022$]. Increases in mood across days were statistically non-significant [$b = 0.051$, 95%CI [–0.039, 0.140], $t_{(26.8)} = 1.112$, $p = 0.276$]. With regard to awake–tired (AT) mood as outcome, subjects became more awake from pre- to post-micro-intervention [$b = 0.514$, 95%CI [0.103, 0.925], $t_{(612.4)} = 2.456$, $p = 0.014$], but not across days [$b = 0.002$, 95%CI [−0.073, 0.077], $t_{(25.5)} = 0.048$, $p = 0.962$]. With regard to calm–nervous (CN) mood as outcome, subjects became calmer from pre- to post-micro-intervention [$b = 0.685$, 95%CI [0.360, 1.010], $t_{(612.3)} = 4.137$, $p < 0.001$], but not across days [$b = -0.018$, 95%CI [−0.088, 0.052], $t_{(26.3)} = 0.502$, $p = 0.620$].

Additional Results Regarding Mood Changes, and Participants' Feedback

Average mood improvements from pre- to post-micro-interventions across day 2 to day 12 were significantly associated with an increase in mood pre-micro-interventions from day 1 to day 13 with regard to GB mood ($r = 0.614$, 95%CI [0.297, 0.809], $p < 0.001$), but not AT mood ($r = 0.279$, 95%CI [−0.122, 0.602], $p = 0.167$) and CN mood ($r = 0.277$, 95%CI [−0.124, 0.601], $p = 0.170$) (calculations based on $n = 26$, due to missing data).

The feedback of the participants ($N = 27$) regarding the number of days of the smartphone-based micro-intervention revealed that 5 subjects (18.52%) agreed that 2 weeks were too short to be successful, while 10 subjects (37.04%) disagreed (the other 12 subjects were neutral); 13 subjects (48.15%) agreed that 2 weeks were well tolerable, while 3 subjects (11.11%) disagreed (the other 11 subjects were neutral). Regarding the duration of the sessions, 8 subjects (29.63%) agreed that the duration was too short to be successful, while 13 subjects (48.10%) disagreed (among which one subject even "strongly disagreed"; the other 6 subjects were neutral); 18 subjects (66.66%) agreed (among which one subject even "strongly agreed") that the duration was well tolerable, while 2 subjects (7.40%) disagreed (among which one subject even "strongly disagreed") (the other seven subjects were neutral). More detailed information on the feedback, as well as respective information based on the sample of participants who at least received the micro-intervention instructions ($N = 30$) with relative frequency of responses virtually identical to those reported here, are provided in Supplementary Material Table 2.

DISCUSSION

The aim of this study was to scrutinize in a real-world setting the use of smartphone-based micro-interventions in form of psychotherapeutic techniques and related changes in mood in a non-clinical sample. We hypothesized that mood improved from pre- to post micro-intervention sessions. Our hypothesis was confirmed. Subjects reported better mood and being calmer and more awake at post- as compared to pre-micro-intervention. However, there was no indication of increases in mood across days. Notably, greater mood improvements (GB mood) from pre- to post-micro-intervention were associated with overall changes in mood from the 1st day until the last day, which would be in line with micro-interventions incrementally improving mood across days if successful on individual days, even though our study design does not allow inferring causality or making assumptions about the long-term stability of the effects. There was no indication that mood improvements from pre- to post-micro-intervention differed between techniques or across the 13 micro-intervention days; hence there was no evidence for habituation of potential micro-intervention effects.

Participants conducted the vast majority of the requested micro-interventions sessions, and only a minority of subjects provided negative feedback regarding the number of micro-intervention days or the duration of the sessions. This indicates that a repeated application of smartphone-based micro-intervention sessions is generally well tolerated. Still, some individuals reported that they would have preferred a higher or lower number of sessions or a longer or shorter training duration, which indicates that personalization also of these parameters

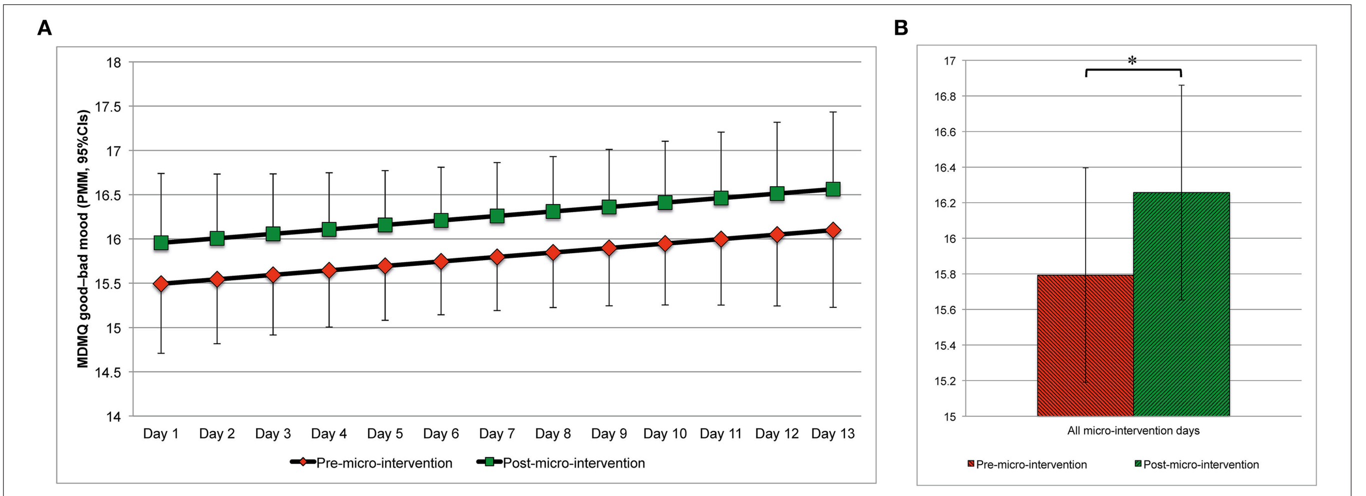

FIGURE 4 | Good–bad mood (predicted marginal means, 95%CIs) pre- and post-micro-intervention, by the micro-intervention day (A) and across all micro-intervention days (B). *$b = 0.464$, 95%CI: 0.068–0.860, $t_{(613.3)} = 2.298$, $p = 0.022$; Higher values indicate better mood; In **(A)**, for the pre-micro-intervention values, the lower boundaries of the 95%CIs are depicted, for the post-micro-intervention values, the upper boundaries of the 95%CIs are depicted; CI, confidence interval; MDMQ, Multidimensional Mood State Questionnaire; PMM, predicted marginal means.

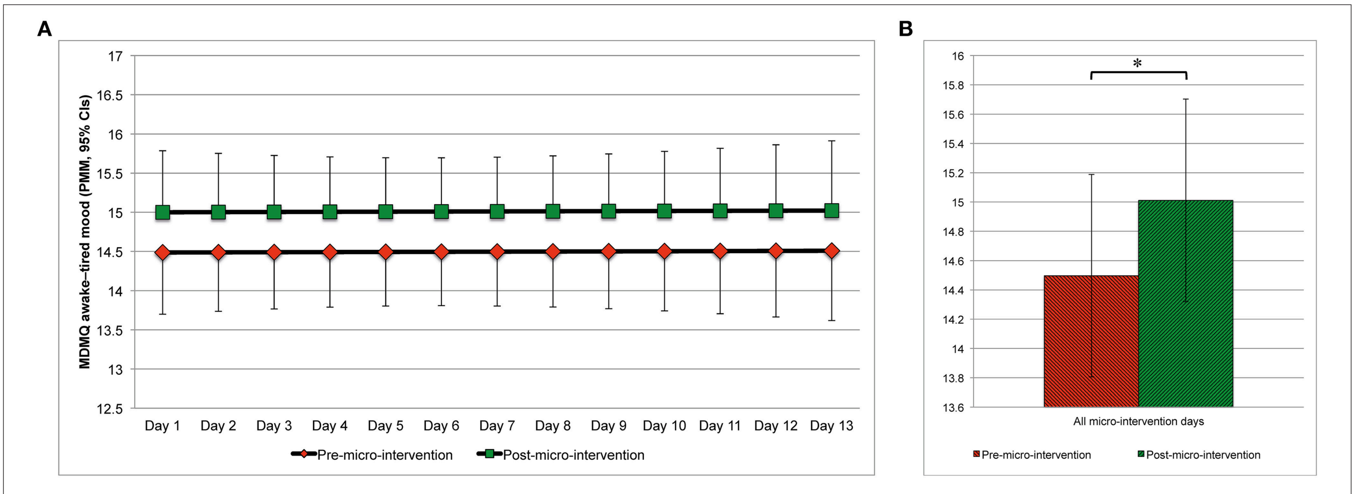

FIGURE 5 | Awake–tired mood (predicted marginal means, 95%CIs) pre- and post-micro-intervention, by the micro-intervention day (A) and across all micro-intervention days (B). *$b = 0.514$, 95%CI: 0.103–0.924, $t_{(612.4)} = 2.456$, $p = 0.014$; Higher values indicate being more awake; In **(A)**, for the pre-micro-intervention values, the lower boundaries of the 95%CIs are depicted, for the post-micro-intervention values, the upper boundaries of the 95%CIs are depicted; CI, confidence interval; MDMQ, Multidimensional Mood State Questionnaire; PMM, predicted marginal means.

may have the potential to further improve the acceptance of smartphone-based micro-interventions.

Our findings extend previous evidence that short-term interventions, using different strategies, can modify mood in non-clinical samples in well-controlled laboratory settings (Velten, 1968; Martin, 1990; Schaefer et al., 2010), by indicating that this holds true when interventions are applied via smartphone in a real-world setting. They are in line with preliminary laboratory-based evidence that smartphone-based interventions can elicit positive mood states (e.g., Cipresso et al., 2012).

With regard to studies with clinical samples assessing psychotherapeutic face-to-face settings, our findings are in line with evidence that mindfulness-based strategies can improve mood and distress (e.g., Brake et al., 2016), even though the current study was only performed on a non-clinical sample of participants. A recent meta-analysis reported that online mindfulness-based intervention programs of 2–12 weeks duration were effective to reduce symptoms of mental disorders, notably with larger effect sizes for interventions of longer duration (Spijkerman et al., 2016). Furthermore, there is preliminary evidence that smartphone-based mindfulness intervention programs, lasting one to several weeks, may improve mood and reduce stress or symptoms of mental disorders (e.g., Brake et al., 2016). Our findings—notably based on a non-clinical sample of participants—are in line with this observation,

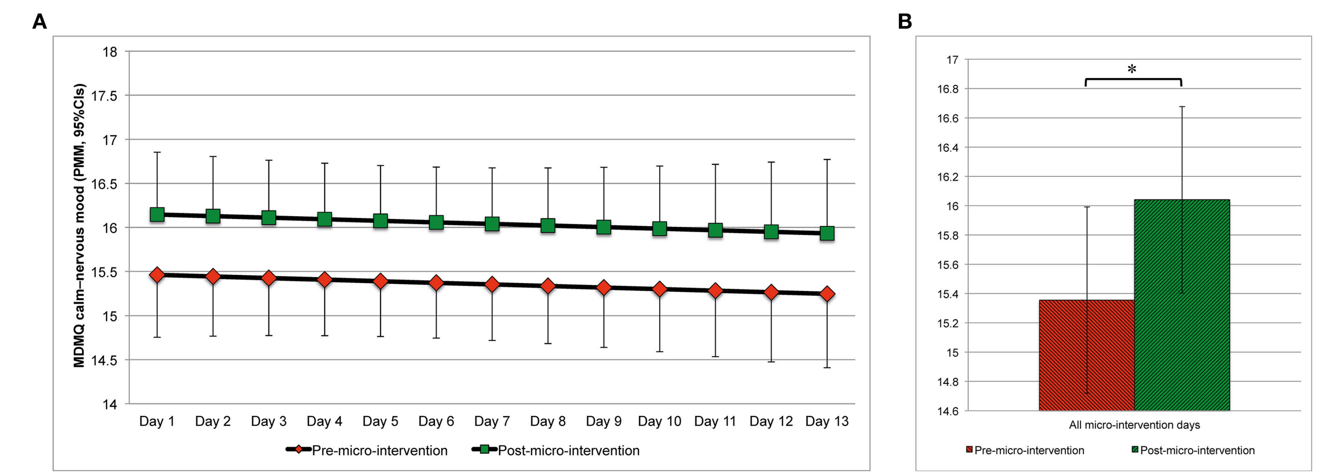

FIGURE 6 | Calm–nervous mood (predicted marginal means, 95%CIs) pre- and post-micro-intervention, by the micro-intervention day (A) and across all micro-intervention days (B). *$b = 0.685$, 95%CI: 0.360–1.010, $t_{(612.3)} = 4.137$, $p < 0.001$; Higher values indicate being calmer; In **(A)**, for the pre-micro-intervention values, the lower boundaries of the 95%CIs are depicted, for the post-micro-intervention values, the upper boundaries of the 95%CIs are depicted; CI, confidence interval; MDMQ, Multidimensional Mood State Questionnaire; PMM, predicted marginal means.

indicating that (i) mindfulness-based micro-interventions of only several minutes duration, applied via smartphone, go along with rapid mood improvements, and (ii) if these interventions are successful during daily individual sessions, they are potentially leading to mood improvements across 2 weeks, even though we cannot make any assumptions about potential longer-term effects. Furthermore, our findings are in line with evidence from the field of smoking cessation, indicating that mobile phones (however, primarily via text messaging), have been successfully used to trigger behavior change (Whittaker et al., 2016). Notably, studies on smartphone-based interventions that target mental health related behavior do not always provide evidence that the interventions have the intended effects; in contrast, some interventions may even lead to opposite effects, at least in subgroups (Gajecki et al., 2014).

Our study design does not allow to disentangle potential processes underlying the mood changes observed in our study, and to identify to which extent different features of the intervention may have contributed to the observed mood changes and the overall good engagement of study participants with the digital intervention. One may speculate that the use of prompts and reminders in our study has improved digital engagement, in line with what has been previously shown (Alkhaldi et al., 2016). Further, consistent with previous evidence, the personal encounter between study personnel and the participants preceding the real-world micro-interventions may have enhanced intervention effects and digital engagement (Palmqvist et al., 2007; Spek et al., 2007; Andersson and Cuijpers, 2009; Richards and Richardson, 2012; Baumeister et al., 2014).

Important strengths of this study include, first, the use of psychotherapeutic techniques for which previous evidence indicated potential to improve stress-related processes; second, the participants' individual selection of their preferred techniques and, third, individual selection of training times; fourth, the use of video-clip supported procedures, ensuring a standardized application of the micro-intervention; and fifth, the use of mixed model analyses, taking into account, amongst others, individual mood variations across days.

There are also limitations. First, we did not include a randomized control condition. Therefore, we cannot determine which factors led to the mood related changes, and we cannot exclude changes in mood driven by digital placebo effects (Torous and Firth, 2016), which, however, is an issue not only in our study but in numerous other studies on the effects of psychotherapeutic interventions (Ioannidis, 2016). Future studies should estimate the effects of micro-interventions on mood within larger randomized controlled trials. Second, the data presented here were collected within a larger study. We cannot finally exclude that our findings were influenced by procedures during the preceding study days. However, there was no statistically significant association between the experimental condition participants were assigned to on experiment day 1 and smartphone-based micro-intervention-related mood changes during the 13 real-world sessions, making it rather unlikely that the randomization within the framework of the larger study was of substantial relevance. Third, the study sample was rather homogenous, with all participants being male and the majority being rather experienced using smartphones. Notably, given that males seek less traditional face-to-face treatment for mental health issues than females (Rhodes et al., 2002), males may be of special interest as target group for alternative interventive approaches. Our findings should be generalized with caution, and future studies are needed that target populations of different cultural backgrounds and more heterogeneous with regard to sex, age, educational background, and digital literacy. Fourth, even though participants were of Korean nationality, having Korean as a first language, written study material was provided in English, which was not adapted or

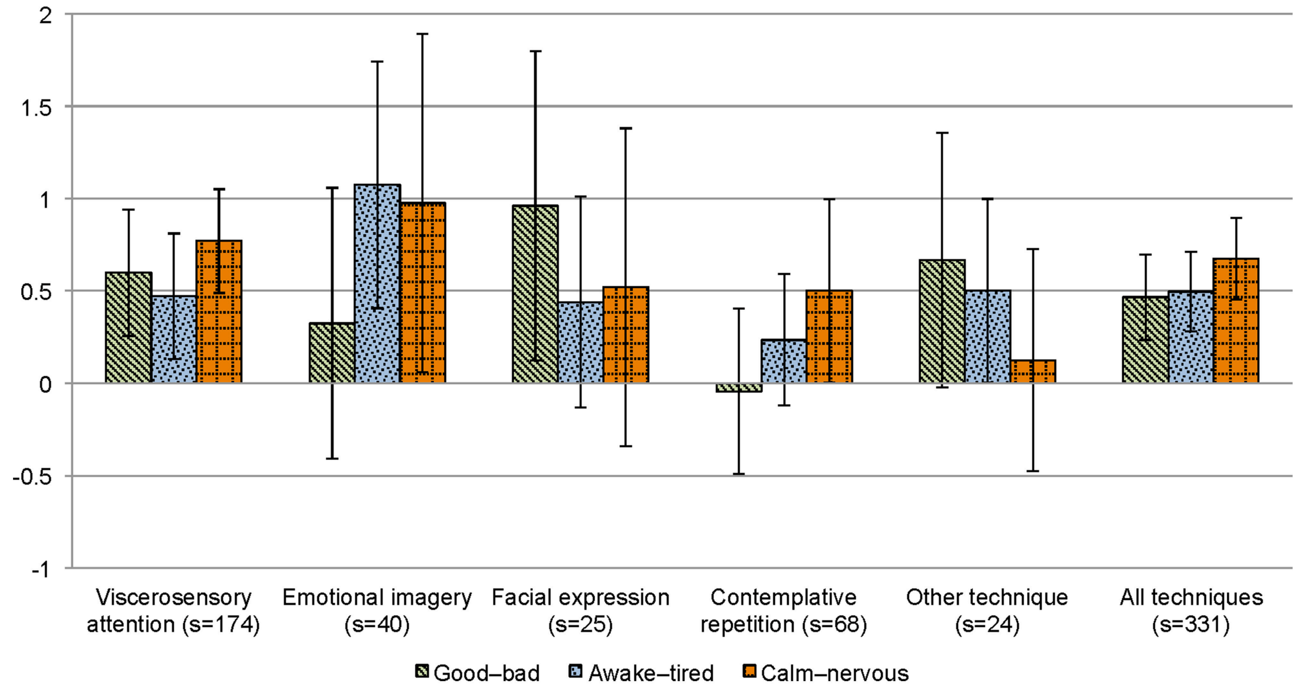

FIGURE 7 | Mood changes (means, 95%CIs) from pre- to post-micro-intervention, stratified according to psychotherapeutic technique. Depending on the scale, higher values indicate better mood, being more awake, and calmer, respectively; CI, confidence interval; s, number of sessions.

normed to the local population. However, all participants had excellent knowledge of written English, and using the English versions of assessment instruments ensured that well-validated versions were applied. Fifth, without follow-up assessment, we cannot draw any conclusion regarding the long-term stability of the mood changes. Finally, we did not randomize the order in which the different techniques were introduced to the participants. Hence, we cannot exclude that order of introduction may have influenced the individual choice of techniques. However, identifying differences in mood changes across psychotherapeutic techniques was not the main goal of our study, and we would have needed a larger sample size and randomized assignment to techniques to further scrutinize this question. Notably, allowing participants to select the technique of their choice increased external validity of our study design, as smartphone-users usually substantially participate in the choice of apps that they apply, and the individual selection may also have improved engagement (Schueller, 2010).

Our findings may have different implications. They suggest the applicability of smartphone-based micro-interventions based on techniques that have been previously applied across a range of therapeutic approaches, including mindfulness-based psychotherapy. If our findings are corroborated in randomized controlled settings and different patient groups, targeted smartphone-based micro-interventions may represent a promising tool to modify mood in real-world settings, as part of more complex behavioral intervention technologies (BITs; Mohr et al., 2014), and complementing other psychotherapeutic interventions within blended treatments (Ly et al., 2015), and in line with the precision medicine approach (Insel, 2014; Collins and Varmus, 2015). Furthermore, they may be used to provide in-the-moment support for non-clinical populations to improve their mood, and allow delivering state-of-the-art psychotherapeutic techniques in a non-stigmatizing fashion to individuals who otherwise would not have access to therapy (Morris et al., 2010).

As mentioned above, future randomized controlled trials are needed to further scrutinize the effects of smartphone-based micro-interventions on mood, including studies addressing in detail the underlying mechanisms. Notably, alternative methodological frameworks, such as the "Continuous Evaluation of Evolving Behavioral Intervention Technologies (CEEBIT)" approach (Mohr et al., 2013b) or the "Person-Based Approach to Intervention Development" (Yardley et al., 2015), may allow evaluating the micro-interventions in different application contexts and help to further tailor applications based on the micro-interventions toward the target user population. In this context, we acknowledge that techniques used in the present study (i.e., the micro-interventions based on video-clips accessed via smartphones) may be considered rather "conventional," in light of the rapid technological advancements made in smartphone technology. More recently, more advanced techniques, such as game-like applications, have been used for delivering smartphone-based psychotherapeutic interventions (e.g., Franklin et al., 2016). However, we also note that the advantage of our approach is that the video-clips can be easily integrated into more complex interventive "apps" (mobile phone applications) or within the contexts of communication routes, for example social media or messenger services (Dinakar et al., 2015). These approaches, with proper steps taken to safeguard information privacy, may confer low-barrier psychosocial interventions. With regard to technological advances, one may also consider combining the approach with the collection of information based on ambulatory biomarkers (Ben Khelil et al., 2011; Tegethoff et al., 2011; Choi et al., 2014), which may allow the application of micro-interventions based on multi-source information. Besides this, future studies should elucidate emerging questions, such as (i) to which extend the mood changes related to the micro-interventions depend on preceding personal contact with the subjects undergoing the micro-intervention, (ii) to which extend mood changes depend on whether subjects self-selected the type of technique applied, and (iii) whether individual mood changes triggered by a micro-intervention session can be predicted by contextual or time factors (Paredes et al., 2014), which will provide a basis for the further personalization of interventions.

Taken together, we provided evidence that smartphone-based micro-interventions are well-tolerated and go along with improvements in mood. In line with the precision medicine approach, smartphone-based micro-interventions may represent a promising tool to modify mood in real-world settings.

AUTHOR CONTRIBUTIONS

GM, JL, SY, and MT designed the study; GM, JL, ES, and MT prepared the study material and data acquisition; JL, ES, MO, EJ, and HK recruited participants and acquired the data; ES, AB, and JA entered the data and prepared it for statistical analyses; GM, ES, and AB analyzed the data; GM, JL, and MT interpreted the data; GM wrote the first draft of the manuscript; GM, JL, ES, AB, MO, EJ, HK, JA, SY, and MT 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.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: http://journal.frontiersin.org/article/10.3389/fpsyg.2016.01112

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The other authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Supplementary Material

Smartphone-based psychotherapeutic micro-interventions to improve mood in a real-world setting

Gunther Meinlschmidt, Jong-Hwan Lee, Esther Stalujanis, Angelo Belardi, Minkyung Oh, Eun Kyung Jung, Hyun-Chul Kim, Janine Alfano, Seung-Schik Yoo, Marion Tegethoff*

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Supplementary Material Data Sheet 1. Brief outline of the larger study from which the data were derived

Study procedure of experiment day 1 and 2 (further details available from the authors on request): Subjects underwent a real-time functional magnetic resonance imaging neurofeedback (RT-fMRI NF) procedure, during which they repeatedly applied previously learned psychotherapeutic techniques inside an magnetic resonance imaging (MRI) scanner. Furthermore, the experiment included a Stroop task, resting periods, repeated blood pressure measurements, ratings on the Self-Assessment Manikin (SAM) scales, and saliva collections. For the RT-fMRI NF experiment only, subjects were randomly assigned to two conditions (details on the randomization procedure available from the authors on request), either the experimental or control condition, with subjects in the experimental condition (n=14 of those included in the main analyses of this article) receiving feedback derived from their own brain activity (blood oxygen level dependent (BOLD) signal) and subjects in the control condition (n=13 of those included in the main analyses of this article) receiving sham feedback (with the feedback signal derived from another subject's brain activity). Subjects were blinded regarding the condition they were assigned to. Neither the RT-fMRI NF procedure nor the randomization to the experimental or control condition is part of the research question of the present publication. Subjects' assignments to experimental or control condition was entered as covariate in some of our statistical analyses (see method section). After the RT-fMRI NF session on experiment day 1, we instructed subjects in how to perform the smartphone-based micro-interventions.

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Supplementary Material Data Sheet 2. Structure and transcript of content of the micro-interventions provided within video-clips (see Supplementary Material Video 1 to 5 for the video-clips themselves)

The total duration of each video-clip is approximately 4 minutes and 40 seconds. The structure of the video-clips is comparable across all psychotherapeutic techniques and contains 4 phases:

1) Each video-clip starts with the display of an instruction text (duration of display approximately 10 seconds): "During the training, you may notice that it is not easy to maintain concentration. Whenever you realize that your thoughts are running away, please just get back to the task and try again. Good luck with the training!"
2) This is followed by a phase in which subjects are asked to apply the psychotherapeutic technique with an instruction text displayed, depending on the technique (duration of phase approximately 120 seconds):
    a. Technique 'viscerosensory attention'; Text displayed: "Your task: Shift your attention towards versus away from bodily sensations, for example your heartbeat, breathing, or feelings in stomach. Keep your attention focused on each sensation for a while."
    b. Technique 'emotional imagery'; Text displayed: "Your task: Imagine emotionally positive, negative or neutral situations, and shift your attention between them, for example think of a beloved person, a stressful exam or a conflict, or a bus ride… Keep your attention focused on each situation for a while."
    c. Technique 'facial expression'; Text displayed: "Your task: Make different emotional expressions with your face and keep each for a while (e.g. happy face, angry face, neutral face)."
    d. Technique 'contemplative repetition'; Text displayed: "Your task: Repeat a short, very easy sentence, or slowly count from 1 to 10 (repeat this over and over again)."
    e. Technique 'other'; Text displayed: "Your task: Remember the strategy that you have successfully practiced in the scanner. Please concentrate and practice this strategy during the next minutes."

   ➔ During this phase, the time until the end of this phase is shown at the bottom right side of the screen and changes every 30 seconds, starting with the display "2 minutes to go", followed by "90 seconds to go", followed by "60 seconds to go", and followed by "30 seconds to go". An hourglass icon at the left of the displayed text illustrates that the text refers to the remaining time.

The end of this phase is indicated by the text: “round 1 finished -- thank you --” (duration of display approximately 4 seconds).

3) This is followed by a short break during which another text is displayed (duration of display approximately 30 seconds, text is scrolling from bottom to top): “Pause: 30 seconds… You have done a great job! You may have noticed that it is not easy to maintain concentration during such a challenging task. Whenever you realize that your thoughts are running away, please just get back to the task and try again. Good luck for the next round!”.
4) This is followed by a phase identical to phase 2 outlined above, with the exception of the end of the phase being indicated by the text: “Congratulations, you have finished today’s training!” (duration of display approximately 4 seconds).

The beginning and end of phases 2 and 4 are signalized by the sound of two high-pitched gongs at approximately 1.7 seconds interval. During phases 2 and 4, images illustrating the respective techniques are shown as background images (see information provided with Supplementary Material 2 to 6 above), while the instruction text is displayed in black font with white outline for the techniques ‘viscerosensory attention’ and ‘other’, and technique instruction text displayed in white font with black outline for the techniques ‘emotional imagery’, ‘facial expression’, and ‘contemplative repetition’, and text to indicate the end of the phases displayed in white font with black outline. During phases 1 and 3, the background screen is dark blue, with text displayed in white font.

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Supplementary Material Data Sheet 3. Additional information regarding the videos provided as 'Supplementary Material Video 1 to 5'

Video to guide through the micro-intervention 'Viscerosensory attention': Video-format: Video encoded via Moving Picture Experts Group (MPEG)-4 Part 10, Advanced Video Coding (MPEG-4 AVC; "H.264"); duration: approximately 4 minutes and 40 seconds); Please note: The background picture displayed during this video is a modified version of *Male with organs* by *Mikael Häggström*, available via Wikimedia commons under the Creative Commons CC0 1.0 Universal Public Domain Dedication; retrieved from: https://commons.wikimedia.org/wiki/File:Male_with_organs.png

Video to guide through the micro-intervention 'Emotional imagery': Video-format: Video encoded via MPEG-4 AVC; duration: approximately 4 minutes and 40 seconds; Please note: The background picture displayed during this video is a modified version of *Meditation in Wat Khung Taphao* by *Tevaprapas*, available via Wikimedia commons under the Creative Commons Attribution 2.5 Generic license; retrieved from: https://commons.wikimedia.org/wiki/File:Meditation_in_Wat_Khung_Taphao.jpg

Video to guide through the micro-intervention 'Facial expression': Video-format: Video encoded via MPEG-4 AVC; duration: approximately 4 minutes and 40 seconds; Please note: The background picture displayed during this video is a modified version of *Haitian Grill (8131305206)* by *Alex Proimos*, available via Wikimedia Commons under the Creative Commons Attribution 2.0 Generic license; retrieved from: https://commons.wikimedia.org/wiki/File:Haitian_Grill_(8131305206).jpg

Video to guide through the micro-intervention 'Contemplative repetition': Video-format: Video encoded via MPEG-4 AVC; duration: approximately 4 minutes and 40 seconds; Please note: The background picture displayed during this video is a modified version of *Mantras caved into rock in Tibet* by *Nathan Freitas*, available via Wikimedia Commons under the Creative Commons Attribution-Share Alike 2.0 Generic license; retrieved from: https://commons.wikimedia.org/wiki/File:Mantras_caved_into_rock_in_Tibet.jpg

Video to guide through the micro-intervention ‘Other technique’: Video-format: Video encoded via MPEG-4 AVC; duration: approximately 4 minutes and 40 seconds; Please note: The background picture displayed during this video is a modified version of *Nicolas P. Rougier's rendering of the human brain* by *Nicolas Rougier*, available via Wikimedia Commons under the GNU General Public License; retrieved from: https://commons.wikimedia.org/wiki/File:Nicolas_P._Rougier%27s_rendering_of_the_human_brain.png?uselang=de

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Supplementary Material Table 1. Information on mobile devices, operating systems (OS), and Internet browsers used for micro-intervention participation[1] (*N*=27).

Variable	Category	*n* (%)[2]
Smartphone type		
	Samsung[3]	15 (55.56%)
	iPhone[4]	6 (22.22%)
	LG[5]	3 (11.11%)
	Nexus 7	1 (3.70%)
	SKY[6]	2 (7.40%)
OS		
	Android[7]	21 (77.78%)
	iOS[8]	6 (22.22%)
Internet browser		
	Chrome[9]	19 (70.37%)
	Android browser	5 (18.52%)
	Safari 6	3 (11.11%)

[1]*In case subjects used different smartphone types, OS, or Internet browsers across micro-intervention session days, we report information on the most common used combination of the three characteristics.*
[2]*Percentages may not total 100 due to rounding*
[3]*The following models were used: Samsung Galaxy S2 (SHW-M2505, SHW-M250K, SHV-E110S), Samsung Galaxy S3 (SHV-E210K, SHV-E210S, SHV-210L), Samsung Galaxy Note (SHV-E160K, SHV-E160L), and Samsung Galaxy Note 2 (SHV-E250K, SHV-E250L)*
[4]*No detailed information regarding iPhone models available*
[5]*The following models were used: LG-F220K Optimus GK and LG-F160K Optimus*
[6]*The following models were used: SKY Vega (IM-A8105) and SKY Vega Racer (IM-A770K)*
[7]*The following OS versions were used: Android 2.3.6, Android 4.0.4, Android 4.1.1, and Android 4.1.2*
[8]*The following OS versions were used: iOS 6 and iOS 7*
[9]*The following browser versions were used: Chrome 18, Chrome 28, Chrome 29, and Chrome 30*

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Supplementary Material Table 2. Participants feedback regarding the micro-intervention, based on the main sample, consisting of participants that conducted at least 3 micro-intervention sessions (*N*=27), and based on the sample of participants that received at least the micro-intervention instructions (*N*=30).

		N=27		*N*=30	
Variable	**Category**	***n***	**(%)***	***n***	**(%)***
"Two weeks of ambulatory training were too short to be successful."	Strongly agree	0	(0%)	0	(0%)
	Agree	5	(18.52%)	5	(16.67%)
	Neutral	12	(44.44%)	15	(50.00%)
	Disagree	10	(37.04%)	10	(33.33%)
	Strongly disagree	0	(0%)	0	(0%)
"Two weeks of ambulatory training were well tolerable."	Strongly agree	0	(0%)	0	(0%)
	Agree	13	(48.15%)	13	(43.33%)
	Neutral	11	(40.74%)	12	(40.00%)
	Disagree	3	(11.11%)	5	(16.67%)
	Strongly disagree	0	(0%)	0	(0%)
"Approximately 10 minutes of ambulatory training per day were too short to be successful."	Strongly agree	0	(0%)	0	(0%)
	Agree	8	(29.63%)	8	(26.67%)
	Neutral	6	(22.22%)	7	(23.33%)
	Disagree	12	(44.44%)	14	(46.67%)
	Strongly disagree	1	(3.70%)	1	(3.33%)
"Approximately 10 minutes of ambulatory training per day were well tolerable."	Strongly agree	1	(3.70%)	1	(3.33%)
	Agree	17	(62.96%)	17	(56.67%)
	Neutral	7	(25.93%)	9	(30.00%)
	Disagree	1	(3.70%)	2	(6.67%)
	Strongly disagree	1	(3.70%)	1	(3.33%)

**Percentages may not total 100 due to rounding.*

Supplementary Material

Smartphone-based psychotherapeutic micro-interventions to improve mood in a real-world setting

Gunther Meinlschmidt, Jong-Hwan Lee, Esther Stalujanis, Angelo Belardi, Minkyung Oh, Eun Kyung Jung, Hyun-Chul Kim, Janine Alfano, Seung-Schik Yoo, Marion Tegethoff*

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Supplementary Material Table 3. Characteristics of the sample of all subjects receiving micro-intervention instructions (*N*=30).

Categorical variables			
Variable	**Category**	***n***	**(%)***
Marital status			
	Single	22	(73.33%)
	In a relationship	8	(26.67%)
Highest degree			
	High school or equivalent	27	(90%)
	Bachelor's degree	3	(10%)
Size of household (including participant**)			
	1	2	(6.90%)
	2	0	(0%)
	3	1	(3.45%)
	4	23	(79.31%)
	5	3	(10.34%)
"I am very experienced in using smartphones"			
	Strongly agree	8	(26.67%)
	Agree	16	(53.33%)
	Neutral	4	(13.33%)
	Disagree	1	(3.33%)
	Strongly disagree	1	(3.33%)

Continuous variables			
Variable (unit)	**Mean**	**(*SD*)**	**Range [min, max]**
Age (years)	24.28	(2.27)	[19.75, 28.70]
Full time education (years)	15.1	(1.37)	[12, 18]
Training participation (days)	11.4	(3.38)	[1, 13]

**Percentages may not total 100 due to rounding; **Information from one subject missing*
Abbreviations: max, maximum; min, minimum; SD, standard deviation.

Supplementary Material

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Supplementary Material Table 4. Additional results in form of interaction effects of mixed model analyses predicting mood (*Number of observations*=667).

Good–bad mood						
Parameter	***beta***	***SE***	**95%CI [LB, UB]**	***t***	***df***	***p*-value**
pre- to post-micro-intervention × micro-intervention day	-0.056	0.054	[-0.162, 0.050]	-1.042	613.6	0.298
pre- to post-micro-intervention × technique: contemplative repetition vs. viscerosensory attention	-0.632	0.537	[-1.685, 0.421]	-1.176	613.1	0.240
pre- to post-micro-intervention × technique: other vs. viscerosensory attention	-0.144	0.468	[-1.062, 0.773]	-0.309	613.3	0.758
pre- to post-micro-intervention × condition	-0.105	0.404	[-0.898, 0.688]	-0.259	613.3	0.796
Awake–tired mood						
Parameter	***beta***	***SE***	**95%CI [LB, UB]**	***t***	***df***	***p*-value**
pre- to post-micro-intervention × micro-intervention day	-0.036	0.056	[-0.146, 0.074]	-0.644	612.7	0.520
pre- to post-micro-intervention × technique: contemplative repetition vs. viscerosensory attention	-0.248	0.558	[-1.342, 0.846]	-0.444	612.1	0.657
pre- to post-micro-intervention × technique: other vs. viscerosensory attention	0.094	0.486	[-0.859, 1.046]	0.193	612.4	0.847
pre- to post-micro-intervention × condition	-0.097	0.420	[-0.921, 0.726]	-0.231	612.3	0.817
Calm–nervous mood						
Parameter	***beta***	***SE***	**95%CI [LB, UB]**	***t***	***df***	***p*-value**
pre- to post-micro-intervention × micro-intervention day	-0.024	0.044	[-0.111, 0.064]	-0.535	612.6	0.593
pre- to post-micro-intervention × technique: contemplative repetition vs. viscerosensory attention	-0.236	0.441	[-1.100, 0.629]	-0.534	612.2	0.593
pre- to post-micro-intervention × technique: other vs. viscerosensory attention	-0.190	0.384	[-0.943, 0.563]	-0.494	612.3	0.621
pre- to post-micro-intervention × condition	-0.297	0.332	[-0.948, 0.355]	-0.893	612.3	0.372

Notes: CI, confidence interval; LB, lower bound; SE, standard error; UB, upper bound.

Supplementary Material

Smartphone-based psychotherapeutic micro-interventions to improve mood in a real-world setting

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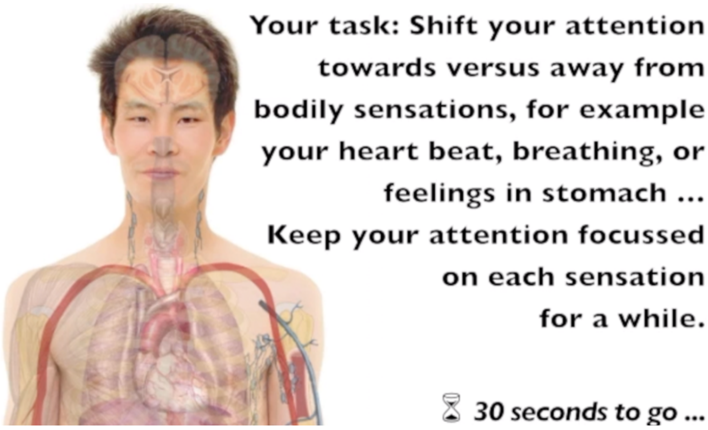
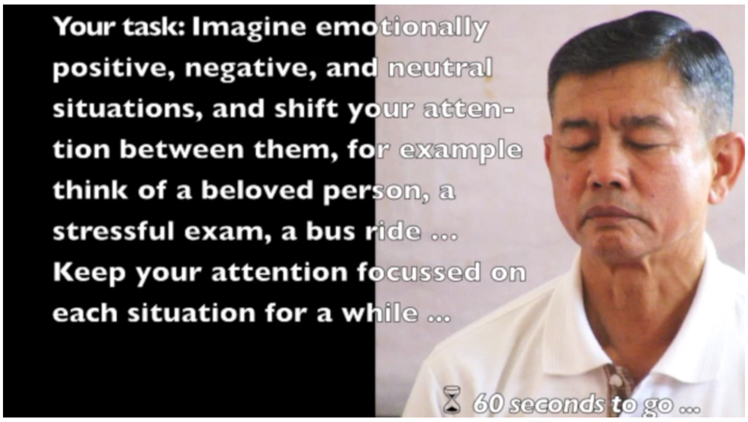
The pictures presented here are screenshots taken from the original video clips used in the study and serve for illustration purposes of micro-interventions strategies. Original video clips are available on: https://www.frontiersin.org/articles/10.3389/fpsyg.2016.01112/full.

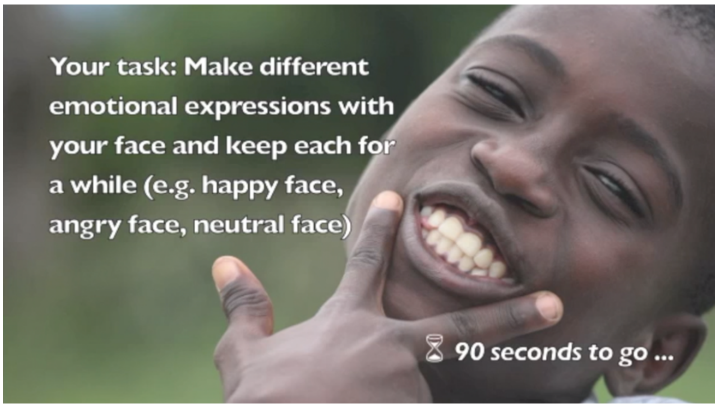
Body attention:



Emotional imagery:

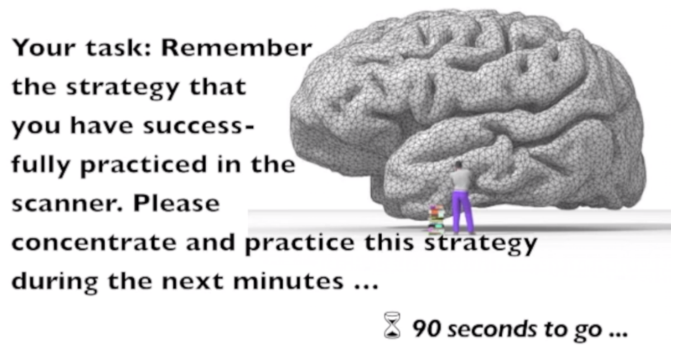


Facial expression:



Mantra:

Individual strategy:



Publication 2: Personalized Prediction of Smartphone-Based Psychotherapeutic Micro-Intervention Success Using Machine Learning

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Research paper

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

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ABSTRACT

Background: Tailoring healthcare to patients' individual needs is a central goal of precision medicine. Combining smartphone-based interventions with machine learning approaches may help attaining this goal. The aim of our study was to explore the predictability of the success of smartphone-based psychotherapeutic micro-interventions in eliciting mood changes using machine learning.

Methods: Participants conducted daily smartphone-based psychotherapeutic micro-interventions, guided by short video clips, for 13 consecutive days. Participants chose one of four intervention techniques used in psychotherapeutic approaches. Mood changes were assessed using the Multidimensional Mood State Questionnaire. Micro-intervention success was predicted using random forest (RF) tree-based mixed-effects logistic regression models. Data from 27 participants were used, totaling 324 micro-interventions, randomly split 100 times into training and test samples, using within-subject and between-subject sampling.

Results: Mood improved from pre- to post-intervention in 137 sessions (initial success-rate: 42.3%). The RF approach resulted in predictions of micro-intervention success significantly better than the initial success-rate within and between subjects (positive predictive value: 0.732 (95%-CI: 0.607; 0.820) and 0.698 (95%-CI: 0.564; 0.805), respectively). Prediction quality was highest using the RF approach within subjects (rand accuracy: 0.75 (95%-CI: 0.641; 0.840), Matthew's correlation coefficient: 0.483 (95%-CI: 0.323; 0.723)).

Limitations: The RF approach does not allow firm conclusions about the exact contribution of each factor to the algorithm's predictions. We included a limited number of predictors and did not compare whether predictability differed between psychotherapeutic techniques.

Conclusions: Our findings may pave the way for translation and encourage scrutinizing personalized prediction in the psychotherapeutic context to improve treatment efficacy.

1. 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, 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

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0165-0327/

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.

2. 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 0800 h and 0300 h 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 we 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.

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

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]

Abbreviations: max, maximum; min, minimum; SD, standard deviation.
[a] Percentages may not total 100 due to rounding.
[b] Information from one subject missing.

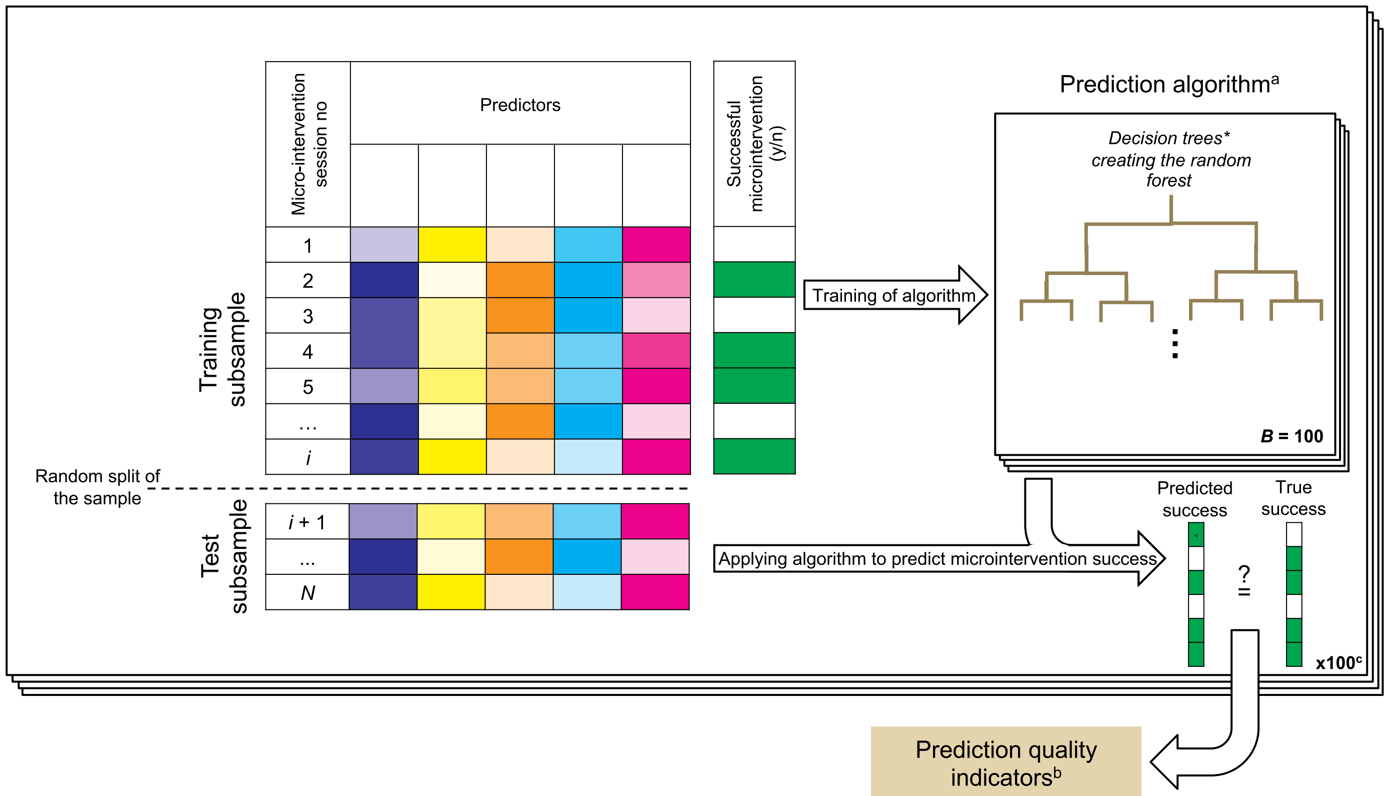

Fig. 1. Outline of the RF-based supervised learning classification problem and prediction quality estimation approach.
[a]RF-based prediction algorithms, using tree-structured fixed-effects predictor functions in mixed-effects logistic regression models; [b]Prediction quality indicators: positive predictive 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 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.*

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 Fig. 1), where the goal was to predict each session's success (outcome 'successful micro-intervention'; dichotomous) using the above-mentioned predictor variables.

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 Fig. 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, Eq. (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).

3. Results

The flowchart of participants is provided in Fig. 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 Fig. 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).

4. 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 subjects 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 subjects 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

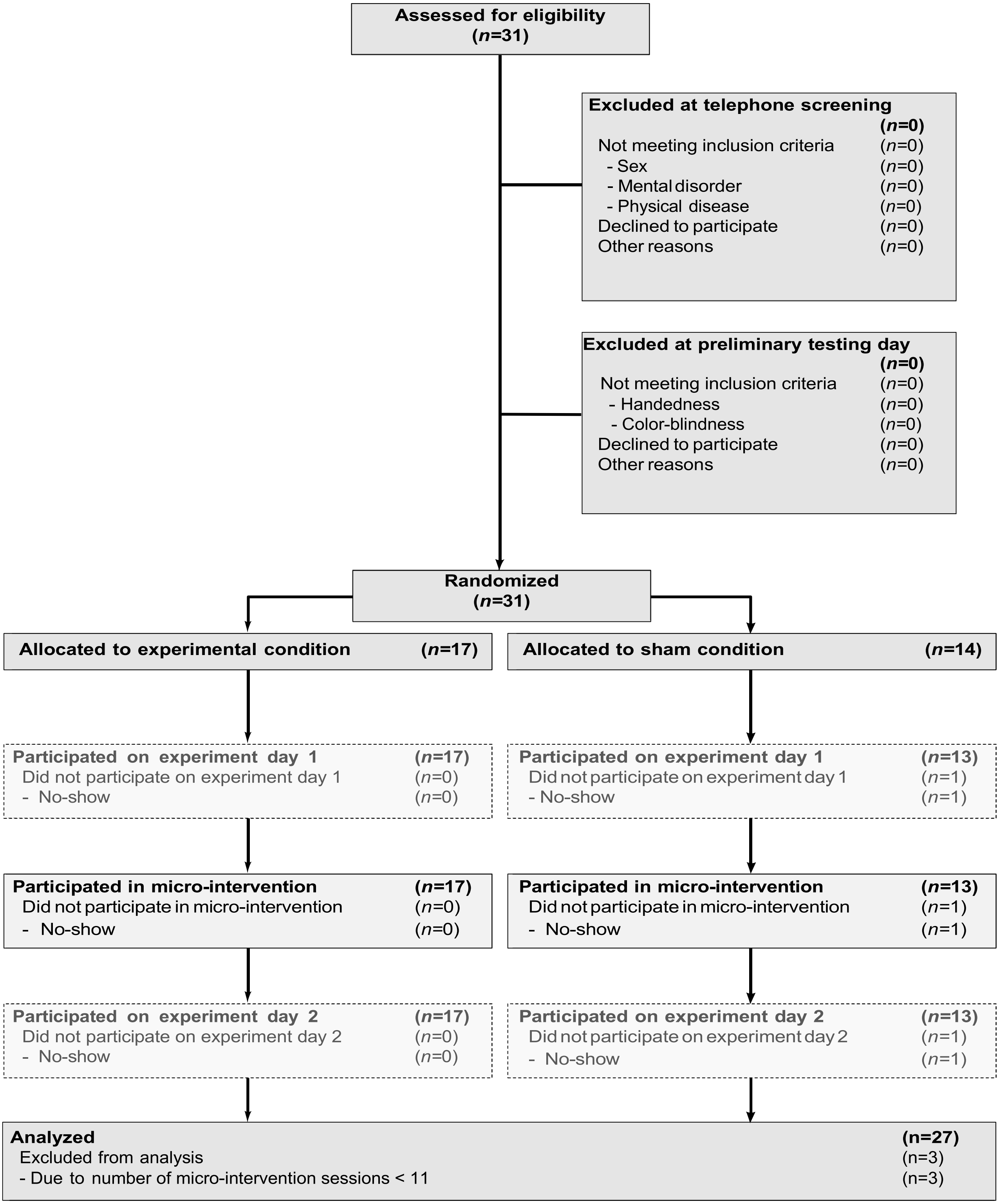

Fig. 2. Participant flow through study.

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,

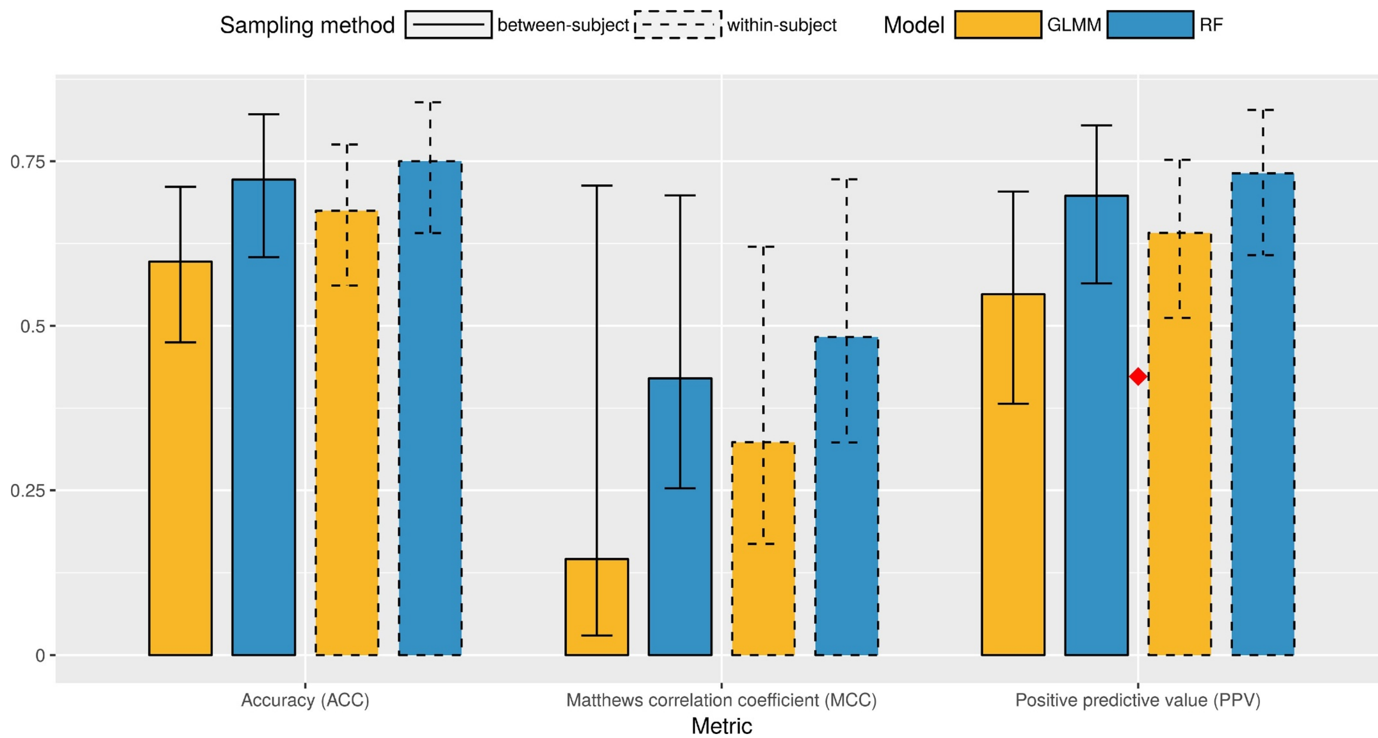

Fig. 3. Quality indicators of prediction of intervention success across prediction models (means and 95% CIs).
Note: The small diamond on the right indicates the initial response rate (42.3%). Results based on 324 micro-intervention sessions. We applied two different subsampling schemes: 1) a between-subject 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.

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

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.

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

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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CRediT authorship contribution statement

Gunther Meinlschmidt: Conceptualization, Methodology, Funding acquisition, Project administration, Formal analysis, Supervision, Visualization, Writing - original draft, Writing - review & editing. **Marion Tegethoff:** Conceptualization, Methodology, Funding acquisition, Project administration, Supervision, Writing - original draft, Writing - review & editing. **Angelo Belardi:** Methodology, Data curation, Formal analysis, Visualization, Writing - review & editing. **Esther Stalujanis:** Methodology, Investigation, Data curation, Formal analysis, Writing - review & editing. **Minkyung Oh:** Investigation, Writing - review & editing. **Eun Kyung Jung:** Investigation, Writing - review & editing. **Hyun-Chul Kim:** Investigation, Writing - review & editing. **Seung-Schik Yoo:** Conceptualization, Writing - review & editing. **Jong-Hwan Lee:** Conceptualization, Methodology, Funding acquisition, Investigation, Methodology, Project administration, Software, Supervision, Writing - review & editing.

Declaration of Competing Interest

None.

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Original Paper
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Induction of Efficacy Expectancies in an Ambulatory Smartphone-based Digital Placebo Mental Health Intervention: Randomized Controlled Trial

Abstract
Background: There is certain evidence on the efficacy of smartphone-based mental health interventions. However, mechanisms of action remain unclear. Placebo effects contribute to the efficacy of face-to-face mental health interventions, and may also be a potential mechanism of action in smartphone-based interventions.
Objectives: We investigated whether different types of efficacy expectancies as potential factors underlying placebo effects could be successfully induced in a smartphone-based digital placebo mental health intervention, ostensibly targeting mood and stress.
Methods: We conducted a randomized, controlled, single-blinded superiority trial with a multi-arm parallel design. Participants underwent an Android-based smartphone-based digital placebo mental health intervention for 20 days. We induced prospective efficacy expectancies via initial instructions on the purpose of the intervention and retrospective efficacy expectancies via feedback on the success of the intervention at days 1, 4, 7, 10, and 13. 132 healthy participants were randomized to a prospective expectancy only (n=33), a retrospective expectancy only (n=33), a combined expectancy (n=34), or a control condition (n=32). As endpoint, we assessed changes in efficacy expectancies with the Credibility Expectancy Questionnaire, before the intervention and on days 1, 7, 14, and 20. For statistical analyses, we used a random effects model for the intention-to-treat sample, with intervention day as time variable and condition as two factors: prospective expectancy (yes vs. no), and retrospective expectancy (yes vs.no), allowed to vary over participant and intervention day.
Results: Credibility (b = -1.63, 95%confidence interval (CI) [-2.37, -0.89], P < .001) and expectancy (b = -0.77, 95%CI [-1.49, -0.05], P = .04) decreased across intervention days. For credibility and expectancy, we found significant three-way interactions intervention day*prospective expectancy*retrospective expectancy (b = 2.05, 95%CI [0.60, 3.50], P = .006 resp. b = 1.55, 95%CI [0.14, 2.95] P = .03), suggesting that efficacy expectancies decreased least in the combined expectancy condition and the control condition.

Conclusions: To our knowledge, this is the first empirical study investigating whether efficacy expectancies could be successfully induced in a specifically designed placebo smartphone-based mental health intervention. Our findings may pave the way to diminish or exploit digital placebo effects and help to improve efficacy of digital mental health interventions.
Registration: ClinicalTrials.gov Identifier: NCT02365220. Registered February 18, 2015.

Keywords: digital placebo effect; efficacy expectancies; EMA; mHealth; prospective expectancy; retrospective expectancy; RCT; smartphone-based intervention

Introduction

Mental disorders are highly prevalent and cause a high global burden of disease [1,2]. A large proportion of persons with mental disorders do not receive adequate treatment, among others due to the limited availability of face-to-face psychotherapy, particularly in low- and middle-income countries [3]. To address these challenges, the World Health Organization (WHO) has defined research priorities to improve the lives of people with mental disorders [4]. One of these research priorities is the development of mobile and IT technologies to increase access to evidence-based care. Furthermore, a substantial part of persons with mental disorders does not respond to traditional face-to-face psychotherapy [5]. Therefore, new forms of treatment are required [6].

Numerous health-related smartphone apps have been applied, for instance, for prevention and treatment of depressive or anxiety disorders [7-10]. Research on the efficacy and effectiveness of these apps is only at its beginning. Recent meta-analyses of randomized controlled trials (RCTs) reported small to moderate effect sizes, suggesting that delivering psychological treatment with smartphone-based devices may be an efficacious approach to treat, for instance, anxiety and depressive symptoms [11,12]. However, there is a lack of knowledge on the potential mechanisms of change of mental health interventions delivered by smartphone apps. Firth and colleagues [11] found that effect sizes of smartphone interventions were smaller in studies with active control conditions, as compared to waitlist/inactive controls, suggesting that the use of a smartphone itself may provide psychological benefit. In this regard, Torous and Firth [13] claimed to consider consequences of a potential placebo effect and introduced the concept of a ‘digital placebo effect’, defined as ‘placebo-like effects seen from mobile health interventions, such as smartphone apps’ (p. 101).

The placebo effect is understood as a range of positive changes occurring after patients have been provided with an inert or inactive treatment [14]. Traditionally, placebo effects are discussed in the field of blinded RCTs in which study participants in a control group receive placebos in the form of inert pills or sham procedures. Active treatments need to outperform placebos in RCTs to be considered effective. In this context, placebo effects should be minimized to ensure a valid investigation of the drug’s efficacy [15].

An important factor underlying placebo effects are outcome expectancies of patients, that means, a therapeutic intervention can produce a placebo effect because the person receiving the treatment believes it will have an effect [14,16]. Previous studies found positive associations between favorable outcome expectancies of patients and positive therapeutic effects for a wide range of medical conditions and mental disorders, such as Parkinson’s disease, hypertension, depression, anxiety, and pain [16-20]. Accordingly, some authors claimed that placebo effects should be maximized to improve treatment outcomes by enhancing patients’ expectancies [15,20]. Gruszka and colleagues [21] stated that despite its therapeutic potential, the validation of efficacy of placebo interventions, such as expectancy interventions, has been neglected. Mobile apps provide a novel approach to provide highly standardized expectancy interventions in a blinded manner and comprise several advantages to investigate expectancy interventions [21].

In sum, there is the urgent need to i) further scrutinize smartphone-based mental health interventions in the context of the WHO grand challenge on the development of mobile and IT technologies to increase access to evidence-based care, ii) explore potential mechanisms of change underlying smartphone-based mental health interventions that are already widespread however little validated, and iii) scrutinize and exploit efficacy expectancies as a potential factor underlying placebo effects, by means of smartphone-based interventions with respect to their methodological advantages.

Previous studies in the context of digital placebo effects introduced the concept [13], focused on methodological recommendations for RCTs of smartphone-based interventions [21,22] or utilized a sham version of an active app as control condition [23]. However, to the best of our knowledge, no study investigated efficacy expectancies as a potential mechanism of the digital placebo effect in a particularly designed inert smartphone-based mental health intervention. Therefore, the aim of our study was to investigate whether efficacy expectancies could be successfully induced in a smartphone-based placebo mental health intervention. We designed a smartphone-based placebo mental health intervention, lasting 20 consecutive days and induced different efficacy expectancies regarding the effects of the intervention on mood and stress in participants, with emotional state being associated with major depression and anxiety as the most frequent mental disorders [1,24]. We differentiated between 'prospective expectancy', which we induced at the beginning of the smartphone-based placebo mental health intervention, and 'retrospective expectancy', which we induced during several days, immediately after participants had completed the smartphone-based digital placebo mental health intervention. We hypothesized that trajectories of efficacy expectancies throughout the smartphone-based placebo mental health intervention differed between conditions. Furthermore, we hypothesized that efficacy expectancies were highest in the combined expectancy condition, followed on a comparable level in the prospective expectancy condition and the retrospective expectancy condition, and lowest in the control condition.

Methods

Overall study procedure

We report the results of a randomized, controlled, single-blinded superiority trial with a multi-arm parallel design, registered at ClinicalTrials.gov (Identifier: NCT02365220). The aim of this larger study was to investigate the placebo effect in a smartphone-based mental health intervention. The Institutional Review Board of the Department of Psychology of the University of Basel, Switzerland, approved the study protocol (no.: 005-14-2). All participants gave written informed consent in accordance with the Declaration of Helsinki. The study was conducted between February and October 2015 at the Department of Psychology of the University of Basel, Switzerland. The study consisted of an introductory session and 20 consecutive days of ambulatory smartphone-based intervention (see Multimedia Appendix 2). The data presented here were collected at the introductory session and on intervention days 1, 7, 14, and 20, when efficacy expectancies had been measured with the Credibility and Expectancy Questionnaire (CEQ; for further details see below).

Introductory session

In the introductory session, we informed participants about the aim and procedure of the study, and assessed inclusion criteria, sociodemographic information, and information on their general and mental health (Patient Health Questionnaire – German version [25,26], Perceived

Stress Scale – 10-items version [27,28]). Irrespective of potential condition assignment, we informed all participants that in our study we would be interested in how mood and perceived stress fluctuated in daily life, and whether smartphones would be suitable to assess their temporal trajectories. We instructed participants to download and install the *ohmage* app [29] from the Google Play Store on their Android-based smartphones. *Ohmage* is an open mobile system consisting of a smartphone application for self-reported data collection and a server system for web-based data storage, management, and administration. We set up and maintained our own *ohmage* server at the IT division of the Department of Psychology.

Smartphone-based digital placebo mental health intervention

The second part of the study consisted of a 20-days smartphone-based ambulatory mental health intervention. Participants started with the intervention three days after they had attended the introductory session. The detailed procedure of each session is being illustrated in Multimedia Appendix 2. The placebo mental health intervention consisted of a green picture or a mock sound, delivered in a video file on EFS Survey which participants accessed via their Android-based smartphones. The videos lasted for two minutes each and alternated daily between green color and mock sound. Regarding the mock sound, we told participants in the initial instructions that the sound would be a very soft tone acoustically not perceivable for the human ear and completely innocuous. On intervention days 1, 4, 7, 10, and 13, we asked participants to take a self-portrait with their smartphone camera within the *ohmage* app. After this second self-portrait, we provided participants with written feedback regarding the self-portrait in the *ohmage* app which we had programmed in advance. On intervention days 1, 7, 14, and 20, we asked participants to rate efficacy expectancies, measured with the CEQ (for further details see below).

Induction of efficacy expectancies

Efficacy expectancies in the four conditions were induced via two ways: 1) the instructions on the purpose of the study on intervention day 1 and 2) the written feedback following the second (i.e., post-placebo-intervention) self-portrait on intervention days 1, 7, 14, and 20. While the initial instructions in our experiment served to induce prospective expectancies in participants, the feedback on the self-portraits served to induce retrospective expectancies (see Figure 1 for fourfold table of the four conditions): 1) Control: on intervention day 1, participants received the identical information about the purpose of the study like in the introductory session, according to which were interested in how mood and perceived stress fluctuated in daily life, and whether smartphones were suitable to assess their temporal trajectories. Regarding the self-portraits, we did not give any explanation on their purpose. After having sent the post-placebo-intervention self-portrait, participants received a 'Thank you' message from us. 2) Prospective expectancy only: on intervention day 1, we told participants that we were interested whether a smartphone-based intervention lasting several weeks might have a positive effect on mood and stress perception. Moreover, we explained that previous studies had demonstrated that green light and soft tones beyond acoustic detection threshold had positively affected the activity of certain brain regions, for instance, the insular lobe. We provided further details on the role of the insular lobe in the formation of unpleasant emotions and the release of stress hormones. We told participants that we assumed that daily exposure to a green picture or an inaudible sound would positively affect their mood and perceived stress in general and their ratings of emotional pictures in particular. Regarding the self-portraits, the procedures were identical to the control condition. 3) Retrospective expectancy only: initial instructions on the purpose of the study were identical to the control condition. Regarding the self-portraits, we told participants that the *ohmage* app would compare the emotional facial expression of the two self-portraits which might differ according to the levels of mood and perceived stress. After having taken the post-placebo-intervention self-portrait, participants were informed by the *ohmage* app that their picture was currently being analyzed. Then, we provided participants with feedback that their stress level and mood had improved to a certain extent. We had programmed the reported levels of improvement for mood and perceived stress in advance. They were identical for each participant, however different for each self-portraying intervention day to make the deception more plausible. 4) Combined expectancy condition: initial instructions on the purpose of the study were identical to the prospective expectancy only condition. Procedures regarding the analysis of the self-portraits were identical to the retrospective expectancy only condition (for detailed instructions see Multimedia Appendix 3).

	No prospective expectancy	Prospective expectancy
No Retrospective expectancy	Control (n=32)	Prospective expectancy only (n=33)
Retrospective expectancy	Retrospective expectancy only (n=33)	Combined expectancy (n=34)

Figure 1. Fourfold table of different conditions

Outcome variable: efficacy expectancies with the Credibility and Expectancy Questionnaire (CEQ) [30]

We measured efficacy expectancies as outcome variable with the Credibility and Expectancy Questionnaire (CEQ) that has been developed to measure treatment expectancy and rationale credibility in clinical outcome studies [30]. Further details on the structure of the CEQ and how we built the subscales credibility and expectancy can be found in [31]. The CEQ shows good psychometric properties [30]. It was administered at the introductory session (day 0) and on intervention days 1, 7, 14, and 20, after participants had completed the smartphone-based mental health intervention and the IAPS picture ratings.

Participants

We recruited participants from the Bachelor student body of the University of Basel, Switzerland, in Psychology and other lectures, where we presented our study. Advertisements of our study were posted on the website of the psychology students' Facebook group and on local bulletin boards of the Department of Psychology. We compensated Psychology students with signatures for study completion, which they required as parts of their Bachelor's studies. If participants dropped out before completion, compensation was granted proportionally. For students of other faculties, we offered participation in a lottery drawing for a tablet computer as compensation. For study participation, students had to use their own smartphones for 20 consecutive days. We included only participants with access to an Android-based smartphone, because the app we used in our study was available for Android only, i.e. potentially interested participants with iOS-based smartphones could not be included in the study. Due to low recruitment rates during initial data collection, students with access to an Android-based tablet computer were also accepted for participation in our study (7 participants in total). The following inclusion criteria applied: no severe visual impairment, no dyschromatopsia, no severe defective hearing, no regular intake of medication (e.g., antidepressants), and no severe mental disorders (e.g., schizophrenia, other psychotic disorders, or severe affective disorders).

Randomization and masking

Participants who met inclusion criteria were randomly assigned to one of the four conditions, as well as to whether they would start the ambulatory smartphone-based placebo exposure by either green color or mock sound, resulting in eight groups (1:1:1:1:1:1:1:1). Randomization was stratified by sex and included a randomly permuted block procedure with fixed block sizes of 8, 16, and 24 participants. To account for the presumably higher percentage of female participants, the female strata included six blocks grouped into two pairs of three blocks, each of them containing one block for each of the three block sizes, whereas the male strata included only three blocks, one block for each block size. Randomization was done in RStudio (Version 0.99.891; R Project for Statistical Computing [32]) by an independent party. Participants were enrolled and assigned to the different conditions by two Master's students, according to predefined rules of a standard operating procedure, which included the utilization of predefined impersonal standard e-mails resp. SMS for inviting and reminding participants to study participation. In cases of unexpected events, the Master's students communicated via e-mail with participants, which was reduced to a necessary extent. Eligible participants were blinded to their allocation. At the end of intervention day 20, we debriefed participants via *ohmage* app on the actual aims of the study and that we had exposed them to a placebo intervention.

Statistical analyses

We estimated the sample size using *a priori* power analysis. As no comparable RCTs were available in the literature, our assumptions regarding effect sizes were speculative. We assumed that a sample size of 30 participants in each condition (120 participants in total) would be required to detect small to moderate effects on a two-sided 5% level of significance and a power of 80%. As we anticipated an exclusion rate of 10%, we intended to assess at least 132 students for eligibility.
For descriptive analyses of baseline characteristics, we calculated absolute frequencies for categorical variables as well as means and standard deviations, and ranges for continuous variables, each separated by condition as well as for the total number of participants (Table 1).
For descriptive analyses of the CEQ as outcome measure, we first inspected histograms and Q-Q-plots for normality. As visual inspection delivered ambiguous results, we conducted Shapiro-Wilk test, which was significant for credibility (W=0.97, P<.001) and expectancy (W=0.95, P<.001), indicating not normally distributed data. Thus, we calculated medians and interquartile ranges (Table 2)
For our main analyses, we applied linear mixed models, taking into account individual variations in efficacy expectancies across days and accommodating missing data. For the calculation of the two subscales credibility and expectancy of the CEQ, we equalized the six items of the CEQ to values from 1 to 9 according to [31], and then calculated the row sums for each subscale. We split the four different conditions into two factors consisting of two levels each: prospective expectancy condition (yes vs. no) and retrospective expectancy condition (yes vs. no), and we entered these variables separately into the models. The variable 'intervention day' was logarithmized with base 10 and centered. Each of the two subscales of the CEQ was entered as outcome variable in separate linear mixed-effects models [33], to estimate changes in credibility or expectancy across intervention days, depending on condition. For our main analyses, we entered the following predictors into the models: i) 'intervention day' (dimensional, days 0, 1, 7, 14, 20, logarithmized with base 10 and

centered), ii) ‘prospective expectancy’ (yes vs. no), iii) ‘retrospective expectancy’ (yes vs. no), as well as the interactions of ‘intervention day’ with ‘prospective expectancy’ and ‘retrospective expectancy’. We entered random intercept and random slope parameters as this improved model fit, the latter assessed based on Akaike’s Information Criterion (AIC) [33], allowing time trajectories of participants to vary per participant and intervention day. With respect to our hypothesis, we were especially interested in a condition x time interaction effect (three-way interaction as condition was entered as two separate variables). We checked residual plots for linearity and normal distribution of residuals.
In additional analyses, we conducted separate linear mixed models each controlling for the effects of either ‘prospective expectancy or ‘retrospective expectancy’. When controlling for ‘prospective expectancy’, we conducted separate models for cases with ‘prospective expectancy’ respectively without, and the predictors i) ‘intervention day’ and ii) ‘retrospective expectancy’, as well as the interaction of ‘intervention day’ with ‘retrospective expectancy’. Likewise, when controlling for ‘retrospective expectancy’, we conducted separate models for cases with ‘retrospective expectancy’ respectively without, and the predictors i) ‘intervention day’ and ii) ‘prospective expectancy’, as well as the interaction of ‘intervention day’ with ‘prospective expectancy’.
We calculated 95% confidence intervals (CIs) using the Wald method. For our mixed model analyses, we included all subjects of the intention-to-treat population (see Figure 2).
We conducted all tests two-tailed and set the level of significance at .05. We used the statistical software package RStudio (Version 0.99.891; R Project for Statistical Computing [32]) for all data analyses and statistical testing, including the package to conduct the mixed models ‘lme4’ [34]. For data preparation and descriptive statistics, we used the packages ‘haven’ [35], ‘dplyr’ [36], ‘tidyr’ [37], ‘car’ [38], ‘ggplot2’ [39], ‘lsmeans’ [34], ‘lmerTest’ [40], and ‘data.table’ [41].

Results

Participant flow

The flow of participants is presented in Figure 2, according to the Consolidated Standards of Reporting Trials (CONSORT) [42]. Out of 140 participants who were assessed for eligibility, eight were excluded before randomization because they did not meet inclusion criteria or for other reasons (e.g. technical problems with their Android-based smartphones). In total, we included 132 participants in our intention-to-treat analyses.

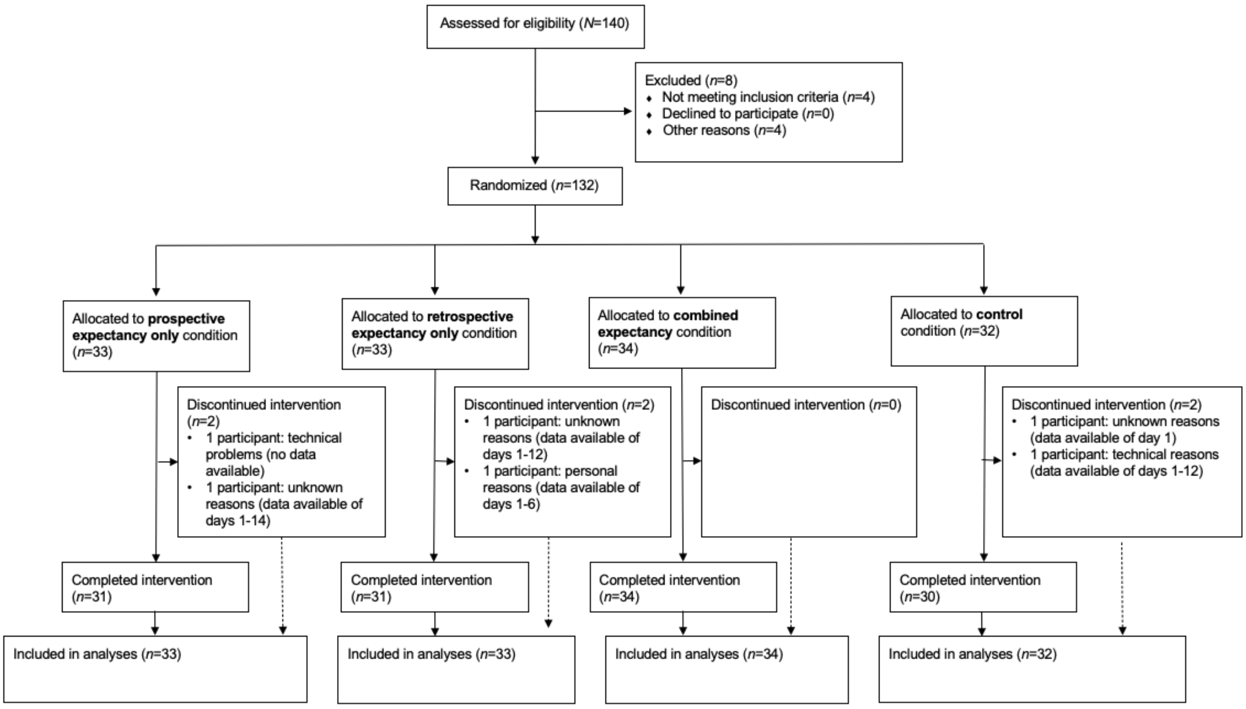

Figure 2: Flow of study participants
Note. As part of our intention-to-treat analyses, we included all study participants in our main analyses who were randomized to one of the four conditions.

Baseline characteristics of study participants

Baseline characteristics of study participants are presented in Table 1.

Table 1. Baseline characteristics of participants included in the analyses

Variable	**Category**	**Condition**				
		Combined (n=34)	Prospective (n=32)	Retrospective (n=33)	Control (n=32)	Total (N=131[a])
Categorical variables		***n***	***n***	***n***	***n***	***N***
Sex						
	Male	4	5	5	5	19
	Female	30	27	28	27	112
Age group						
	18-24	32	28	26	27	113
	25-29	0	2	2	3	7
	30-39	1	2	3	2	8
	40 or older	1	0	2	0	3
Nationality						
	Swiss	23	22	22	27	94
	European country	7	3	5	2	17
	Other foreign country	0	0	1	0	1

	Double nationality (either of them is Swiss)	4	7	4	3	18
Education category[b]						
	Vocational education	0	0	1	0	1
	High school diploma[c]	31	30	28	30	119
	University or College degree	3	2	3	2	10
	Other	0	0	1	0	1
Working part-time						
	Yes	19	15	15	19	68
	No	15	17	18	13	6
Relationship status						
	Single	15	16	14	14	59
	In a romantic relationship	18	15	15	18	66
	Married	1	0	3	0	4
	Divorced	0	1	1	0	2
Occurrence of depressive symptoms for the last two weeks[d]		9	8	4	9	30
Occurrence of anxiousness, nervousness, strain, or excessive worriedness for the last four weeks[e]		0	1	0	1	2
Continuous variables		**Mean (SD) Range [min, max])**	**Mean (SD) Range [min, max]**	**Mean (SD) Range [min, max]**	**Mean (SD) Range [min, max]**	**Mean (SD) Range [min, max]**
Full time education (years)		13.7 (2.3) [5, 19]	13.7 (2.5) [5, 22]	14.0 (2.4) [9, 20]	13.7 (2.8) [3, 20]	13.8 (2.5) [3, 22]
Duration to complete the 20 days intervention		23.5 (3.5) [19, 41]	25.1 (8.8) [19, 62]	26.1 (7.2) [19, 50]	23.9 (5.9) [19, 62]	24.6 (6.6) [19, 62]
PSS-10		16.1 (4.8) [6, 26]	15.4 (4.8) [5, 25]	15.2 (6.6) [4, 30]	17.0 (6.9) [4, 32]	15.9 (5.8) [4, 32]

Abbreviations: Combined – combined expectancy condition; Control – control condition; max – maximum; min – minimum; Prospective – prospective expectancy only condition; Retrospective – retrospective expectancy only condition; PSS-10 – Perceived Stress Scale, 10 items version; SD – standard deviation

[a]Even though we included all 132 study participants of the intention-to-treat sample in our main analyses, here, we report the data of 131 study participants because for one study participant, the data presented here was missing.

[b]The categories “no formal education”, “compulsory education”, and “higher vocational education (incl. school for technicians, professional school)” have been dropped due to no cases.

[c]In the German version of the questionnaire, it has been asked for "Matura", the secondary school leaving certificate in Switzerland, equivalent to International Standard Classification for Education (ISCED) 34.
[d]Items of the Patient Health Questionnaire - German version, with the following scale: 1 = Not at all, 2 = On single days, 3 = On more than half of the days, 4 = Almost every day; categorization according to meeting at least the criteria for 'other depressive syndrome' according to PHQ-D manual
[e]Items of Patient Health Questionnaire – German version, with the following scale: 1 = No, 2 = Yes, categorization according to meeting at criteria for panic syndrome or other anxiety syndromes

Results from the mixed model analyses

Credibility

Descriptive statistics can be found in Table 2 and in the interaction plots of Figure 3. Results of the main mixed models are presented in Table 3. We found a significant main effect of intervention day (b = -1.63, 95%confidence interval (CI) [-2.37, -0.89], P < .001), suggesting that credibility decreased over intervention days, irrespective of condition. We found a significant three-way interaction intervention day*prospective expectancy (PE)*retrospective expectancy (RE; b = 2.05, 95%CI [0.60; 3.50], P = .006). Results from additional analyses (see Multimedia Appendix 4) suggest that the significant three-way interaction was driven by two opposite two-way interactions intervention day*RE, one positive in cases with PE (b = 1.18, 95%CI [0.31; 2.05], P = .009) and one negative in cases with no PE (b = -0.87, 95%CI [-2.06; 0.33], P = .15), with 95% confidence intervals of estimates minimally overlapping. When controlling for RE, the two-way interaction pattern intervention day*PE was comparable. In line with Figure 3, these findings suggest that credibility decreased least in the combined expectancy condition and in the control condition.

Table 2. Outcome measures: Median scores of CEQ per intervention day (N=131)[a]

Outcome	**Intervention day**	**Condition**									
		Combined		Prospective		Retrospective		Control		Total	
Credibility		Median (IQR)	*n*	Median (IQR)	*n*	Median (IQR)	*n*	Median (IQR)	*n*	Median (IQR)	*N*
	0	16 (4.75)	34	16 (5.25)	32	16 (4)	33	15 (4.25)	32	16 (4)	131
	1	12.5 (7)	34	14 (5.5)	32	12 (5)	33	12.5 (7.25)	32	13 (7)	131
	7	11.5 (7)	34	11 (8)	32	8 (7)	32	10 (8)	31	10 (8)	129
	14	12.5 (8)	34	9.5 (6.75)	32	8 (6)	31	10 (6.75)	30	9 (8.5)	127
	20	11.5 (6.5)	32	8 (7)	31	7 (7.5)	31	9.5 (8.75)	30	9 (9)	124
Expectancy		Median (IQR)	*n*	Median (IQR)	*n*	Median (IQR)	*n*	Median (IQR)	*n*	Median (IQR)	*N*

	0	11.5 (5.75)	34	12 (4.5)	32	11 (5)	33	10 (7.75)	32	11 (5.25)	131
	1	10.5 (4.75)	34	10 (5.25)	32	9 (4)	33	11 (7.25)	32	10 (6)	131
	7	10 (5)	34	8 (5.25)	32	6 (3.25)	32	8 (5.5)	31	8 (5)	129
	14	8.5 (5)	34	7 (5.5)	32	6 (5.5)	31	7.5 (10)	30	7 (7)	127
	20	7.5 (5.25)	32	7 (3.5)	31	6 (4.5)	31	8.5 (9.75)	30	7 (7)	124

Abbreviations: CEQ – Credibility Expectancy; Combined – combined expectancy condition; Control – control condition; IQR – interquartile range; Prospective – prospective expectancy only condition; Retrospective – retrospective expectancy only condition

[a]Even though we included all 132 study participants of the intention-to-treat sample in our main analyses, here, we report the data of 131 study participants because for one study participant, the data presented here was missing. Means and standard deviations were calculated based on existing values. *N*s per intervention day and condition are given in the table.

Table 3. Results of linear mixed models (*N*=131)[a]

Credibility					
Predictors[b]	*b*	95% CI		*P*	
(Intercept)	11.35	10.04;	12.66	< .001	***
Intervention day (time; log.)	-1.630	-2.37;	-0.89	< .001	***
Prospective expectancy (PE)	0.497	-1.35;	2.34	.60	
Retrospective expectancy (RE)	-0.590	-2.43;	1.25	.53	
Time*PE	-1.130	-2.16	-0.09	.03	*
Time*RE	-0.869	-1.91	0.17	.10	
PE*RE	1.467	-1.11	4.05	.26	
Time*PE*RE	2.046	0.60	3.50	.006	**
Goodness-of-fit					
AIC	3559.2				
Expectancy					
Predictors[b]	*b*	95% CI		*P*	
(Intercept)	9.715	8.45;	10.98	< .001	***
Intervention day (time; log.)	-0.770	-1.49;	-0.05	.04	*
Prospective expectancy (PE)	-0.425	-2.21;	1.36	.64	
Retrospective expectancy (RE)	-1.373	-3.15;	0.40	.13	
Time*PE	-0.871	-1.88;	0.13	.09	
Time*RE	-0.744	-1.75;	0.26	.15	
PE*RE	2.099	-0.39;	4.59	.10	
Time*PE*RE	1.548	0.14;	2.95	.03	*
Goodness-of-fit					

AIC	3378.7				

Abbreviations: AIC – Akaike information criterion; PE – prospective expectancy (yes vs. no); RE – retrospective expectancy (yes vs. no); time – intervention day

[a]We included 132 study participants of the intention-to-treat sample in our dataset. As from one participant there was no data available for at least one intervention day, statistical analyses were conducted with the data of only 131 participants.

[b]For interpretation purpose, we entered the four conditions as two separate variables 'prospective expectancy' (PE; yes vs. no) and 'retrospective expectancy' (RE; yes vs. no) in the mixed models. This means: 'combined expectancy condition' corresponds to PE = yes AND RE = yes; 'prospective expectancy only condition' corresponds to PE = yes AND RE = no; 'retrospective expectancy only condition' corresponds to PE = no AND RE = yes; and 'control condition' corresponds to PE = no AND RE = no.

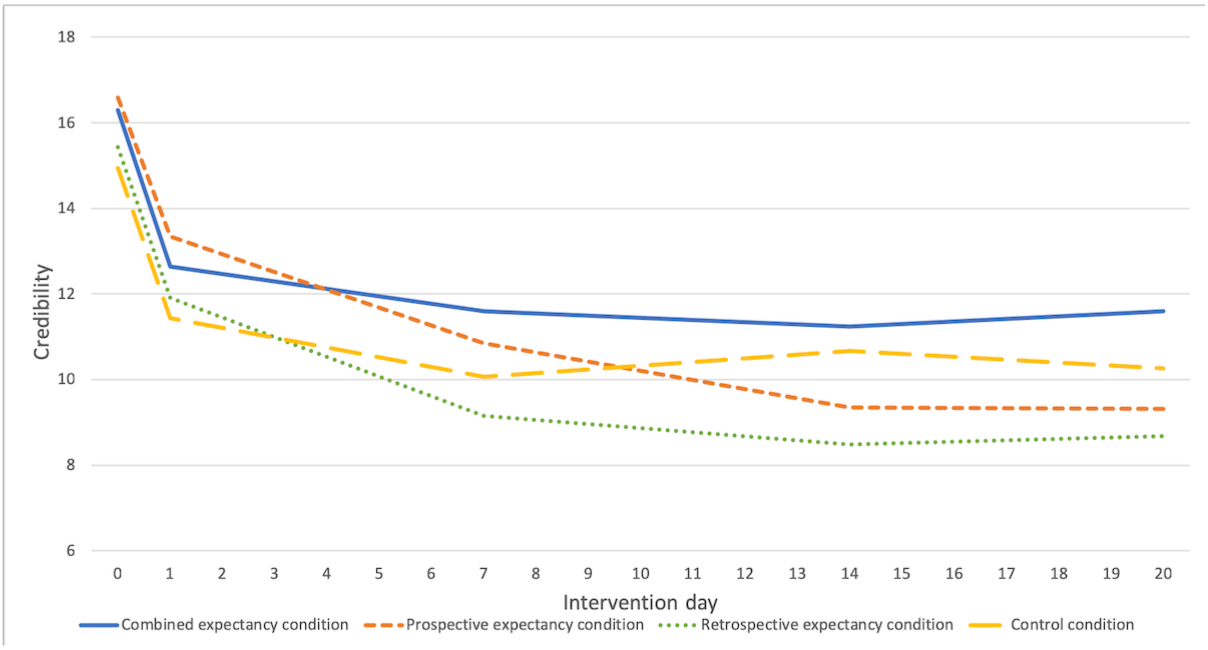

Figure 3. Time trajectories of credibility throughout intervention days (means)
Note. Means were calculated based on existing values. *N*s per intervention day and condition are given in Table 2.

Expectancy

Descriptive statistics can be found in Table 2 and in the interaction plots of Figure 4. Results of the main mixed models are presented in Table 3. We found a significant main effect of intervention day (b = -0.77, 95%CI [-1.49; -0.05], P = .04), suggesting that expectancy decreased over intervention days. We found a significant three-way interaction intervention day*prospective expectancy*retrospective expectancy (b = 1.55, 95%CI [0.14; 2.95], P = .03). Results from additional analyses (see Multimedia Appendix 5) suggest that the significant three-way interaction was driven by two opposite two-way interactions intervention day*RE, one positive in cases with PE (b = 0.81, 95%CI [-0.01; 1.62], P = .05) and one negative in cases with no PE (b = -0.74, 95%CI [-1.92; 0.44], P = .21), with 95% confidence intervals of estimates minimally overlapping. When controlling for RE, the two-way interaction pattern intervention day*PE was comparable. In line with Figure 4, these findings suggest that expectancy decreased least in the combined expectancy condition and in the control condition.

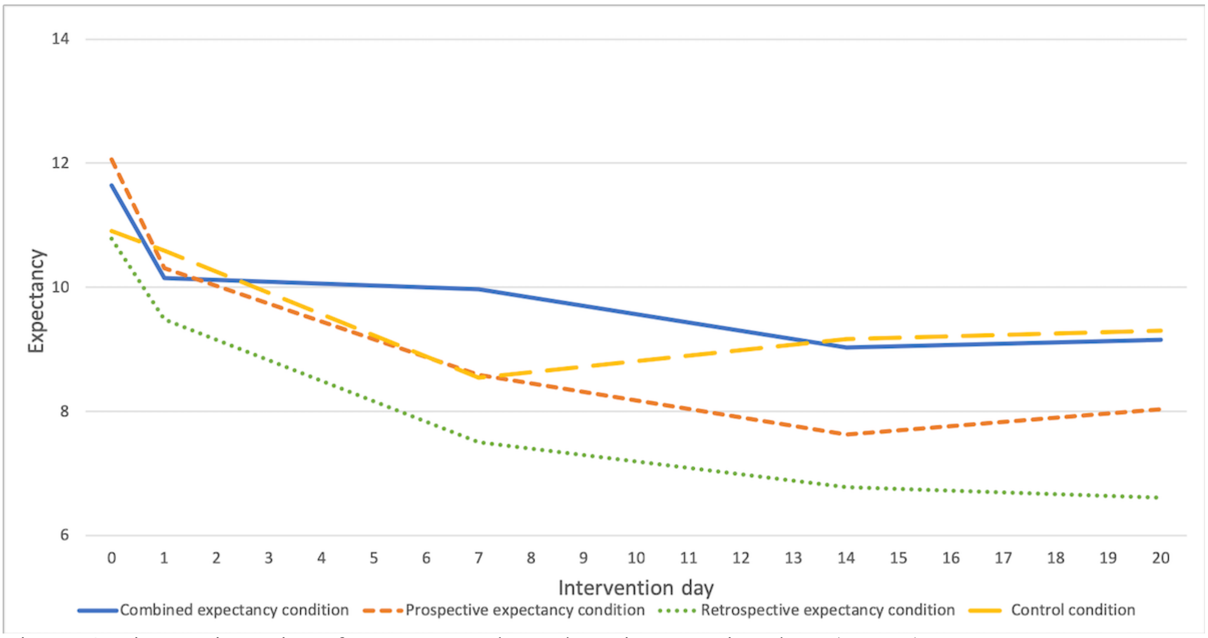

Figure 4. Time trajectories of expectancy throughout intervention days (means)
Note. Means were calculated based on existing values. *N*s per intervention day and condition are given in Table 2.

Discussion

To the best of our knowledge, this is the first empirical study investigating whether efficacy expectancies could be successfully induced in a smartphone-based placebo mental health intervention. We found that efficacy expectancies decreased throughout intervention days, irrespective of condition. Efficacy expectancies decreased least in the combined expectancy and the control condition, most in the prospective expectancy only condition and the retrospective expectancy only condition.

The finding that efficacy expectancies decreased throughout intervention days may partly be explained by the length and monotony of the intervention. Some participants mentioned in their feedback at the end of the intervention that the duration of the smartphone-based intervention and the daily exposure to green color or mock sound were too long.

Efficacy expectancies decreased least in the combined expectancy and in the control condition, followed by the prospective expectancy only and the retrospective expectancy only condition. As displayed in the Figures 3 and 4, the verbal instructions given in the prospective expectancy only condition alone did not seem to have a large effect on efficacy expectancies, as they continued to decrease after intervention day 1, in which the instructions had been given. A potential explanation may be that our verbal instructions were not potent enough to raise efficacy expectancies. Accordingly, Rief and colleagues [43] encouraged study participants of the PSY-HEART study to develop very clear expectancies of how their daily life would change after successful heart surgery. Due to these more personal associations, study participants may have been more convinced of and, thus, may have formed stronger expectancies. Future studies may further explore potential study protocols to maximize expectancies, regarding types (e.g., conditioning procedure instead of verbal instructions [14,16]), timepoint, amount of repetitions and intervals of expectancy induction.

Our study has several strengths: First, we set up the study in the frame of an RCT, the gold standard in psychotherapy research. Second, the smartphone-based placebo intervention, as well as efficacy expectancies, were delivered in a standardized way by providing them in the preprogrammed surveys in the Android-based smartphone app as well as on the online platform, through which heterogeneity due to different experimenters or protocols could be reduced. Although randomization and allocation concealment were not done automatically in the Android-based smartphone app but by experimenters, in most cases, they did not have any personal contact to study participants after randomization, thereby reducing experimenter bias. Third, our results have high ecological validity both by participants using their own smartphones in daily life at a specific time of the day but also from intervention day 15 in situations when they felt stressed. Fourth, by adapting the open-source *ohmage* app to the purpose of our study, we provide a minimal cost intervention which enables fully identical replications as well as their utilization in low- and middle-income countries in which there is a lack of financial resources. Fifth, with the use of mixed model analyses, we took into account individual variations in efficacy expectations across intervention days and accounted for missing data.

Our results may be interpreted in lights of several limitations. First, we designed the smartphone-based intervention in line with the aim of our study to create an inert intervention. We did not focus on making the intervention particularly attractive to study participants, for instance, by integrating elements of gamification [44], which may have affected the decrease in efficacy expectancies throughout the intervention. It may be hypothesized that the time trajectories in efficacy expectancies may differ in a study using a smartphone-based application designed to have a specific effect. Still, in contrast to the "law of attrition", which describes the observation of high rates of discontinuation in eHealth trials [45], we have a high completion rate, with data available for 93% of cases, which makes our findings relatively robust. Second, the study sample was quite homogenous, with most of the participants being female psychology students. As our sample did not consist of a clinical sample, it may rather reflect subjects using smartphone for preventive purposes. Hence, findings may be generalizable rather to populations seeking prevention. Notable, in a clinical population, participants' desire to get an effect out of the intervention are expected to be higher than in a healthy sample, which has been found to modulate placebo analgesia in irritable bowel syndrome patients [46]. Therefore, it may even be easier to induce a digital placebo effect in a clinical sample, as compared to ours, which, however, requires further investigation. Another limitation regarding our sample is that data collection took place in the year 2015 and it would have been preferable using more recent data, particularly in a fast-emerging field like mHealth. However, the latency between data collection and dissemination of findings in our study is comparable to other relevant studies in this field [23,47]. Furthermore, while timely dissemination of findings from clinical trials would be important to base clinical decisions on best scientific evidence, a previous study [48] found that only 29% of completed RCTs of US academic medical centers are published within two years after study completion, indicating that, to reduce publication bias, older data needs to be disseminated, too. Nonetheless, our findings need imminent replication. For replication, it would also be preferable to increase the sample size, which, however, encompassed 132 participants in our main statistical analyses, and, thus, was above the median of comparable RCTs included in two recent meta-analyses ([11,12]. Third, some participants reported technical or usability problems with the *ohmage* app which may have led to a certain level of frustration throughout the course of the intervention, and which may have diminished efficacy expectancies. However, as the reported frequency of technical problems with the app was low (0.6% of all cases), we do not assume that this aspect has reduced the validity of our findings. Fourth, as participants entered the study at different points of time, we cannot exclude that participants who had already finished the study might have informed others about the actual study purpose prior to study completion, which may have reduced the effect of the induction of efficacy expectations particular in the experimental conditions. However, we speculate that this may have affected efficacy expectancies of only few participants, because i) participants might not have remembered and passed all the details of the study design to others; ii) it might have been in the interest of most of the Psychology students to promote the study and iii) students from other fields than Psychology might did not systematically participate and, thus, might not have shared details of the purpose of the study. Fifth, we included only participants with access to an Android-based smartphone which limits the generalizability to iPhone and other operating systems users. However, a recent study found that personality traits (e.g. well-being, self-esteem, optimism, pessimism, and the Big Five) which might affect efficacy expectancies differed only little between iOS and Android users [49].

In this paper, we focused on the investigation of whether we succeeded in inducing efficacy expectancies in a smartphone-based placebo mental health intervention. A required next step would be to investigate whether the induction of efficacy expectancies affected behavioral outcomes, such as mood and stress (Stalujanis et al., in preparation). In the field of placebo research, there are situations in which placebo effects should be diminished and others in which placebo effects should be enhanced [15,21]. Further investigation of time trajectories of efficacy expectancies as a potential mechanism of digital placebo effects may help to improve research on the efficacy of smartphone-based mental health interventions by disentangling digital placebo effects from specific effects. A potential study design may provide participants with a smartphone-based inert intervention until placebo effects are supposed to be flattened and then deploy the actual intervention which may then be less distorted by placebo effects. Additionally, it is well-known that, after initial involvement, users of digital mental health interventions tend to put those away [50]. If smartphone-based mental health interventions work only every second or third time, users may lose their motivation and do not see any gain in the intervention. Personalized prediction of the effects of efficacy expectancies may foster longer-term utilization of smartphone-based interventions. In a previous study, we found that, by using a machine learning approach, predictions of smartphone-based psychotherapeutic micro-interventions success could be improved, as compared to the initial success-rate within and between participants [51]. Future studies should investigate predictors of efficacy expectancies on an intra- and interindividual level to design tailor-made individualized interventions to contribute to further advancement in the growing field of precision medicine [52].

To the best of our knowledge, this is the first empirical study investigating whether efficacy expectancies could be successfully induced in a smartphone-based placebo mental health intervention. We found that efficacy expectancies decreased throughout intervention days. Efficacy expectancies decreased least in a combined expectancy condition and in the control condition, most in a retrospective expectancy only condition and a prospective expectancy only condition. Our findings may pave the way for both diminishing and exploiting effects of outcome expectancies as a potential mechanism of the digital placebo effect and help to improve treatment efficacy of digital mental health interventions.

Acknowledgments

Author's contributions: ES conceptualized and designed the study, acquired data, carried out the statistical analyses, analyzed and interpreted data, drafted the initial manuscript, critically reviewed the manuscript, and approved the final version of the manuscript. JN conceptualized and designed the study, acquired data, analyzed and interpreted data, critically reviewed the manuscript, and approved the final version of the manuscript. MGS conceptualized and designed the study, acquired data, analyzed and interpreted data, critically reviewed the manuscript, and approved the final version of the manuscript. AB analyzed and interpreted data, critically reviewed the manuscript, and approved the final version of the manuscript. MT conceptualized and designed the study, analyzed and interpreted data,

critically reviewed the manuscript, approved the final version of the manuscript, and obtained funding. GM supervised the study as principal investigator, conceptualized and designed the study, acquired data, analyzed and interpreted data, critically reviewed the manuscript, approved the final version of the manuscript, and obtained funding. All authors had full access to all of the data (including statistical reports and tables) in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Conflict of interests: None declared

We thank Professor Deborah Estrin for providing us with very useful hints regarding programming and utilization of *ohmage*.

Abbreviations:
CEQ: Credibility and Expectancy Questionnaire
RCT: randomized controlled trial; WHO – World Health Organization

Multimedia Appendix (Supplemental Files)

Multimedia Appendix 1 [Outline of the larger study] (format: .pdf)
Caption Multimedia Appendix 1: Abbreviations: IAPS – International Affective Picture System

Multimedia Appendix 2 [Study design of the larger study] (format: .pdf)
Caption Multimedia Appendix 2: Abbreviations: CEQ – Credibility Expectancy Questionnaire; IAPS – International Affective Picture System; MDMQ – Multidimensional Mood State Questionnaire; SAM – Self-Assessment Manikin; STAI-6: short form of the Spielberger State-Trait Anxiety Inventory; VAS – visual analog scale

Multimedia Appendix 3 [Instructions of the four conditions of the study] (format: .pdf)
Caption Multimedia Appendix 3: *Note.* The above-listed instructions have been translated from German to English by the first author for illustration purposes. German original versions are available on request by the authors.

Multimedia Appendix 4 [Results of additional analyses of linear mixed models with credibility as outcome (*N*=131)[a]**] (format: .pdf)**
Caption Multimedia Appendix 4:

Abbreviations: AIC – Akaike information criterion; *n obs.* – number of observations; PE – prospective expectancy (yes vs. no); RE – retrospective expectancy (yes vs. no); time – intervention day
[a]We included 132 study participants of the intention-to-treat sample in our dataset. As from one participant there was no data available for at least one intervention day, statistical analyses were conducted with the data of only 131 participants.
[b]For interpretation purpose, we entered the four conditions as two separate variables 'prospective expectancy' (PE; yes vs. no) and 'retrospective expectancy' (RE; yes vs. no) in the mixed models.

Multimedia Appendix 5 [Results of additional analyses of linear mixed models with expectancy as outcome (*N*=131)[a]**] (format: .pdf)**

Caption Multimedia Appendix 5:
Abbreviations: AIC – Akaike information criterion; *n obs.* – number of observations; PE – prospective expectancy (yes vs. no); RE – retrospective expectancy (yes vs. no); time – intervention day
[a]We included 132 study participants of the intention-to-treat sample in our dataset. As from one participant there was no data available for at least one intervention day, statistical analyses were conducted with the data of only 131 participants.
[b]For interpretation purpose, we entered the four conditions as two separate variables 'prospective expectancy' (PE; yes vs. no) and 'retrospective expectancy' (RE; yes vs. no) in the mixed models.

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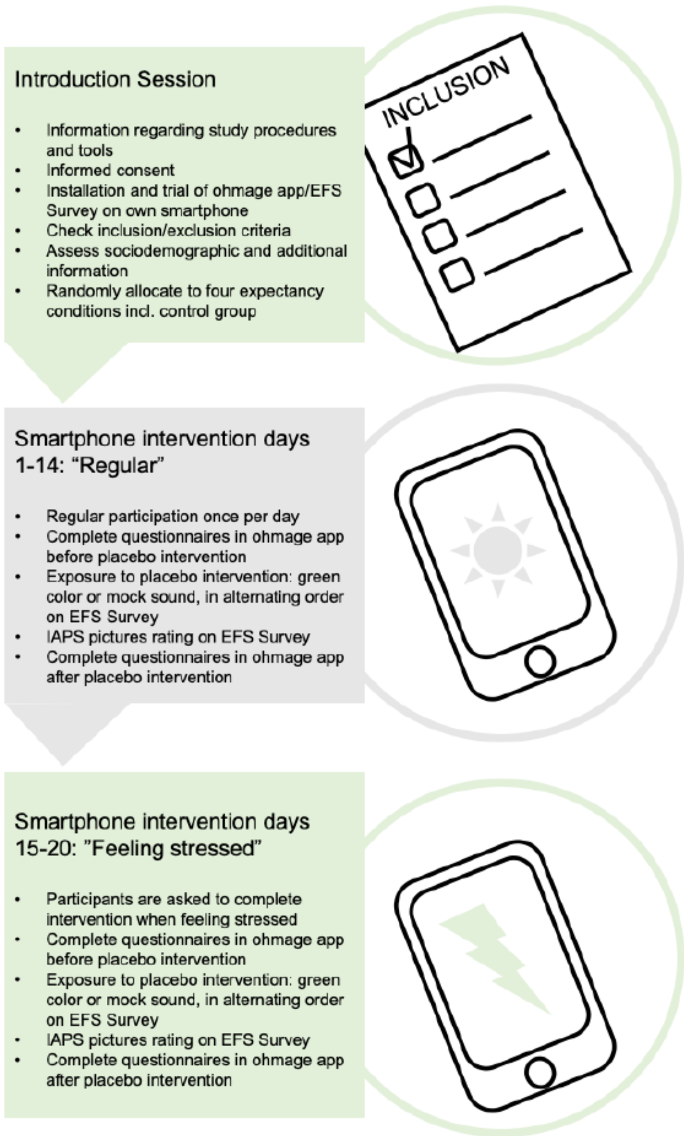
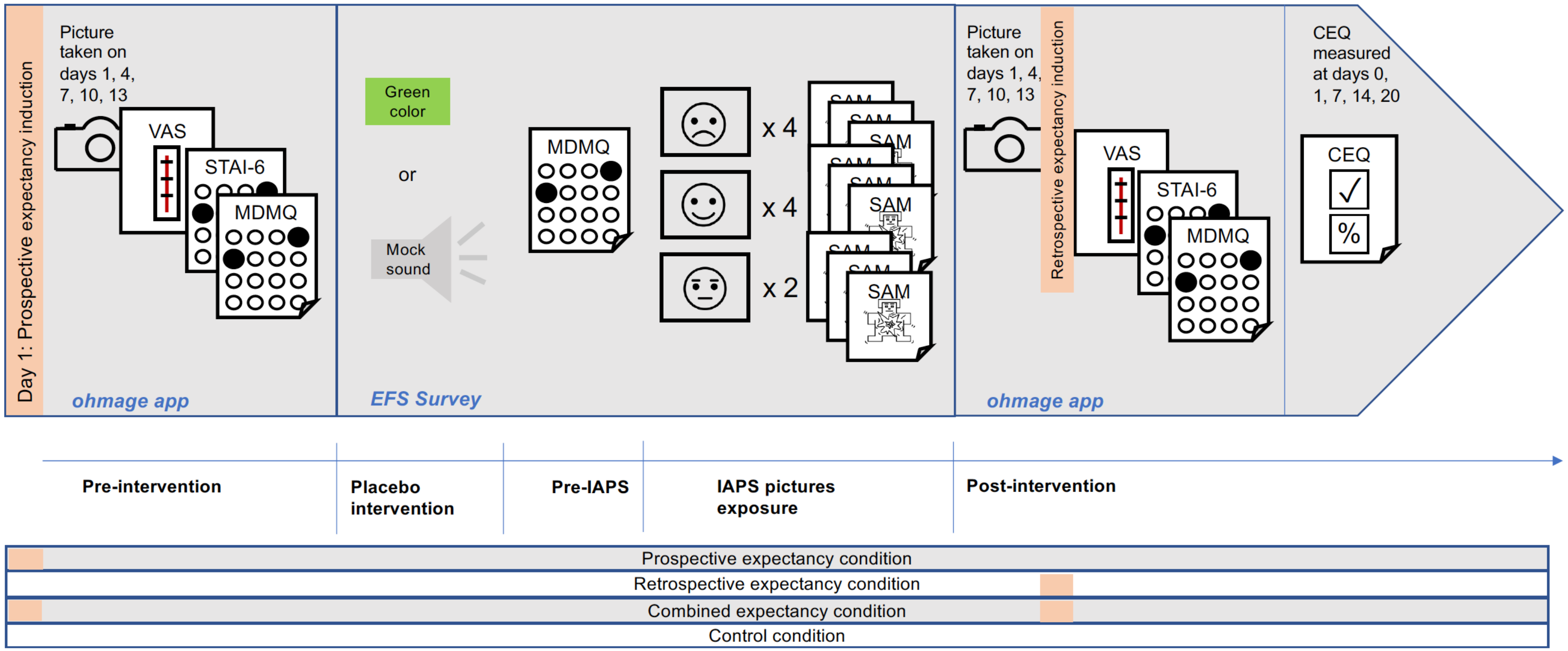
Multimedia Appendix 1. Outline of the larger study



Abbreviations: IAPS - International Affective Picture System

Multimedia Appendix 2: Study design of the larger study



Abbreviations: CEQ – Credibility Expectancy Questionnaire; IAPS – International Affective Picture System; MDMQ – Multidimensional Mood State Questionnaire; SAM – Self-Assessment Manikin; STAI-6: short form of the Spielberger State-Trait Anxiety Inventory; VAS – visual analog scale

Multimedia Appendix 3. Instructions of the four conditions of the study

Condition	**Instruction**
Control	General introduction: *"Thank you for participating in our smartphone study. You help us to find out how mood and perceived stress fluctuate in daily life and whether smartphones are suitable to capture their trajectories."* Intervention day 1: *"Welcome to our smartphone study. We are interested how mood and perceived stress vary in daily life and whether smartphones are suitable to capture their trajectories. During the next three weeks you will complete questionnaires on stress and your mental state and rate affective pictures on a daily basis. Additionally, we will ask you to watch a green picture during two minutes on each day or to open yourself to a non-audible tone on your smartphone. The tone is a very gentle sound, which is not audible for the human ear, and does not pose a danger to your health."* *"On some days, we will additionally ask you to take a self-portrait with your smartphone, before and after the rating of emotional pictures."* Intervention days 1, 4, 7, 10, 13 (pre-intervention): *"Please take a self-portrait with your smartphone camera on the following site by ticking the box with the camera symbol. Your smartphone camera will be turned on automatically. Please be aware that your whole face should be on the picture and try to avoid sudden movements."* *"Fine! Thank you! Please click on 'Next' to continue with the next task."* Intervention days 1, 4, 7, 10, 13 (post-intervention):

	"Please again take a self-portrait with your smartphone camera on the following site by ticking the box with the camera symbol. Your smartphone camera will be turned on automatically. Please be aware that your whole face should be on the picture and try to avoid sudden movements." <u>Intervention days 1, 4, 7, 10, 13 (post-intervention):</u> <u>feedback on self-portrait:</u> *"Thank you very much!"*
Prospective expectancy	<u>General introduction:</u> *"Thank you for participating in our smartphone study. You help us to find out whether daily exposure to green light and a soft tone in the course of a smartphone intervention lasting several weeks may have a positive effect on mood and stress perception."* <u>Intervention day 1:</u> *"Welcome to our smartphone study. We are interested in the effects of a smartphone intervention lasting several weeks on mood and stress perception. During the next three weeks, you will complete questionnaires on stress and your mental state as well as rate affective pictures on a daily basis. Additionally, we will ask you to watch a green picture during two minutes on each day or to open yourself to a non-audible tone on your smartphone. The tone is a very soft sound, which is not audible for the human ear, and does not pose a danger to your health. Previous studies found that green light and soft tones beyond perception threshold may positively affect the activity of certain brain regions, such as the so-called insula. The insula is involved in the formation of unpleasant emotions (e.g. anger, fear, sadness, disgust) and the release of stress hormones, such as cortisol. Therefore, we assume that the daily exposure to a green picture or soft tone will positively affect your mood as well as your stress perception in general and particularly at the rating of emotional pictures."*

"On some days, we will additionally ask you to take a self-portrait with your smartphone, before and after the rating of emotional pictures."

Intervention days 1, 4, 7, 10, 13 (pre-intervention):

Instructions identical to the control condition.

Intervention days 1, 4, 7, 10, 13 (post-intervention):

Instructions identical to the control condition.

Intervention days 1, 4, 7, 10, 13 (post-intervention):

feedback on self-portrait:

Instructions identical to the control condition.

Retrospective expectancy	General introduction: *Instructions identical to the control condition.*

Intervention day 1:

Instructions identical to the control condition, except:

"On some days, we will additionally ask you to take a self-portrait with your smartphone, before and after the rating of emotional pictures. The ohmage app will compare your self-portraits regarding your emotional facial expression, which may vary according to mood and perceived stress. Subsequently, you will receive a short feedback on picture analysis."

Intervention days 1, 4, 7, 10, 13 (pre-intervention):

Instructions identical to the control condition.

Intervention days 1, 4, 7, 10, 13 (post-intervention):

Instructions identical to the control condition, except for:

"Your picture is currently being analyzed. Please click on 'Next' now."

	<u>Intervention days 1, 4, 7, 10, 13 (post-intervention):</u> <u>feedback on self-portrait:</u> <u>Intervention day 1:</u> *"Your stress level and your mood improved about 20 per cent."* <u>Intervention day 4:</u> *"Your stress level and your mood improved about 30 per cent."* <u>Intervention day 7:</u> *"Your stress level and your mood improved about 50 per cent."* <u>Intervention day 10:</u> *"Your stress level and your mood improved about 40 per cent."* <u>Intervention day 13:</u> *"Your stress level and your mood improved about 60 per cent."*
Combined expectancy	<u>General introduction:</u> *Instructions identical to the prospective expectancy condition.* <u>Intervention day 1:</u> *"Welcome to our smartphone study. We are interested in the effects of smartphone intervention lasting several weeks on mood and stress perception. During the next three weeks you will complete questionnaires on stress and your mental state and rate affective pictures on a daily basis.* *Additionally, we will ask you to watch a green picture during two minutes on each day or to open yourself to a non-audible ton on your smartphone. The ton is a very gentle sound, which is not audible for the human ear, and does not pose a danger to your health. Previous studies found that green light and soft tons beyond perception threshold may positively affect the activity of certain brain regions, such as the so-called insula. The insula is involved in the formation of unpleasant emotions (e.g. anger, anxiety, grief, disgust) and the release of stress hormones, such as cortisol. Therefore, we assume that*

daily exposure to green picture or soft ton will positively affect your mood as well as your stress perception in general and particularly at the rating of emotional pictures."

"On some days, we will additionally ask you to take a self-portrait with your smartphone, before and after the rating of emotional pictures. The ohmage app will compare your self-portraits regarding your emotional facial expression, which may vary according to mood and perceived stress. Subsequently, you will receive a short feedback on picture analysis."

<u>Intervention days 1, 4, 7, 10, 13 (pre-intervention):</u>

Instructions identical to the control condition.

<u>Intervention days 1, 4, 7, 10, 13 (post-intervention):</u>

Instructions identical to the control condition.

<u>Intervention days 1, 4, 7, 10, 13 (post-intervention): feedback on self-portrait:</u>

Instructions identical to the retrospective expectancy condition.

Note. The above-listed instructions have been translated from German to English by the first author for illustration purposes. German original versions are available on request by the authors.

Multimedia Appendix 4. Results of additional analyses of linear mixed models with credibility as outcome (*N*=131)[a]

	Model 1: PE = no (*n*=65, *n obs.*=315)					Model 2: PE = yes (*n*=66, *n obs.*=327)				
Predictors[b]	*b*	95% CI		*P*		*b*	95% CI		*P*	
(Intercept)	11.33	10.06;	12.61	< .001	***	11.85	10.48;	13.21	< .001	***
Intervention day (time; log.)	-1.64	-2.50;	-0.79	< .001	***	-2.76	-3.39;	-2.13	< .001	***
Prospective Expectancy (PE)	= 0					= 1				
Retrospective Expectancy (RE)	-0.59	-2.37;	1.20	.51		0.88	-1.02;	2.78	.36	
Time*RE	-0.87	-2.06;	0.33	.15		1.18	0.31;	2.05	.009	**
Goodness-of-fit										
AIC	1765.9					1793.3				
	Model 3: RE = no (*n*=64, *n obs.*=314)					Model 4: RE = yes (*n*=67, *n obs.*=328)				
Predictors[a]	*b*	95% CI		*P*		*b*	95% CI		*P*	
(Intercept)	11.34	9.96;	12.72	< .001	***	10.77	9.52;	12.02	< .001	***
Intervention day (time; log.)	-1.64	-2.46;	-0.82	<. 001	***	-2.49	-3.16;	-1.82	< .001	***
Prospective Expectancy (PE)	0.51	-1.44;	2.45	.60		1.96	0.21;	3.70	.03	*
Retrospective Expectancy (RE)	= 0					= 1				
Time*PE	-1.12	-2.26;	0.03	.06		0.91	-0.02;	1.84	.06	
AIC	1761.7					1802.9				

Abbreviations: AIC – Akaike information criterion; *n obs.* – number of observations; PE – prospective expectancy (yes vs. no); RE – retrospective expectancy (yes vs. no); time – intervention day

[a]We included 132 study participants of the intention-to-treat sample in our dataset. As from one participant there was no data available for at least one intervention day, statistical analyses were conducted with the data of only 131 participants.

[b]For interpretation purpose, we entered the four conditions as two separate variables 'prospective expectancy' (PE; yes vs. no) and 'retrospective expectancy' (RE; yes vs. no) in the mixed models.

Multimedia Appendix 5. Results of additional analyses of linear mixed models with expectancy as outcome (N=131)[a]

	Model 1: PE = no (n=65, *n obs.*=315)					Model 2: PE = yes (n=66, *n obs.*=327)				
Predictors[b]	*b*	95% CI		*P*		*b*	95% CI		*P*	
(Intercept)	9.71	8.45	10.98	< .001	***	9.29	8.00	10.58	< .001	***
Intervention day (time; log.)	-0.77	-1.61	0.07	.07		-1.64	-2.23	-1.06	< .001	***
Prospective Expectancy (PE)	= 0					= 1				
Retrospective Expectancy (RE)	-1.37	-3.15	0.07	.13		0.73	-1.07	2.53	.42	
Time*RE	-0.74	-1.92	0.44	.21		0.81	-0.01	1.62	.05	
Goodness-of-fit										
AIC	1684.7					1693.7				
	Model 3: RE = no (n=64, *n obs.*=314)					Model 4: RE = yes (n=67, *n obs.*=328)				
Predictors[a]	*b*	95% CI		*P*		*b*	95% CI		*P*	
(Intercept)	9.72	8.34	11.11	< .001	***	8.34	7.19	9.49	< .001	***
Intervention day (time; log.)	-0.77	-1.54	0.01	.05		-1.52	-2.19	-0.85	< .001	***
Prospective Expectancy (PE)	-0.43	-2.38	1.52	.66		1.68	0.07	3.28	.04	*
Retrospective Expectancy (RE)	= 0					= 1				
Time*PE	-0.87	-1.96	0.21	.11		0.68	-0.25	1.61	.15	
AIC	1665.0					1718.3				

Abbreviations: AIC – Akaike information criterion; *n obs.* = number of observations; PE – prospective expectancy (yes vs. no); RE – retrospective expectancy (yes vs. no); time – intervention day

[a]We included 132 study participants of the intention-to-treat sample in our dataset. As from one participant there was no data available for at least one intervention day, statistical analyses were conducted with the data of only 131 participants.

[b]For interpretation purpose, we entered the four conditions as two separate variables ‘prospective expectancy’ (PE; yes vs. no) and ‘retrospective expectancy’ (RE; yes vs. no) in the mixed models.

Discussion

Summary and interpretation of the findings

In the first publication of this dissertation, we investigated the applicability of smartphone-based psychotherapeutic micro-interventions evoking mood changes in a real-world setting in a non-clinical sample across 13 days. The findings provide evidence that smartphone-based micro-interventions may be applicable to elicit short-term mood changes. These findings are in line with recent studies investigating the effects of internet- and smartphone-based psychotherapeutic micro-interventions on mood and distress (Elefant et al., 2017) as well as body satisfaction (Fuller-Tyszkiewicz et al., 2019). Publication 1 was already disseminated in 2016. While in the meantime there is a sufficient body of evidence of the efficacy of smartphone apps for the prevention and treatment of mental disorders (Firth, Torous, Nicholas, Carney, Pratap, et al., 2017; Firth, Torous, Nicholas, Carney, Rosenbaum, et al., 2017), and, for instance, specifically standalone smartphone-based ecological momentary interventions (EMIs; Marciniak et al., 2020), there are as yet only a few studies explicitly investigating effects of digital micro-interventions on behavioral outcomes (Bunge et al., 2017; Bunge et al., 2016; Elefant et al., 2017; Fuller-Tyszkiewicz et al., 2019). Thus, the findings of publication 1 are not only relevant because they provide evidence of the applicability of smartphone-based psychotherapeutic micro-interventions eliciting short-term mood changes as one of the first studies in this field, but also in regard to their contribution to shaping the term and concept of micro-interventions, whose relevance has been highlighted in a recently published viewpoint article (Baumel et al., 2020).

To increase the efficacy of smartphone-based micro-interventions, it would be helpful to know whether, when, for whom, and under what conditions micro-interventions work, which leads us to publication 2 of this dissertation. In publication 2, we explored the utility of an ML-based RF algorithm for the prediction of smartphone-based psychotherapeutic micro-interventions success in eliciting mood changes, based on contextual information. As compared to the initial micro-intervention success rate (42.3%), the RF approach resulted in significantly better predictions of micro-intervention success within and between subjects. Predictions based on the more conventional generalized linear mixed-effects models (GLMM) approach were significantly better than the initial success rate only within subjects but not between subjects. These findings extend previous knowledge on the utility of ML-based approaches for the prediction of treatment success in pharmacotherapy and face-to-face psychotherapy, mostly based on neurobiological data (Chekroud et al., 2016; Costafreda et al., 2009; Hoogendoorn et al., 2016; Lueken et al., 2016). Furthermore, the findings from publication 2 encourage the use of data of mobile/wearable sensors in the context of ML-based prognosis, treatment, and support of mental health conditions, in line with previous studies (Banos et al., 2016; Burns et al., 2011; Paredes et al., 2014; Wahle et al., 2016). As yet, there is no comparable study which investigated the applicability of ML for the prediction of smartphone-based psychotherapeutic micro-intervention success regarding improvement of a mental health outcome such as mood. However, authors of a previous study (Alshurafa et al., 2016) used smartphone-based data to predict which patients would benefit from a remote health monitoring system for the promotion of a healthy nutrition and lifestyle to reduce their risk of cardiovascular heart disease. Alshafura and colleagues (2016) based their predictions on one-month data, whereas publication 2 of this dissertation provides evidence that even more timely data (collected at the micro-intervention day or on the day before) may be predictive of micro-intervention success.

In publication 3 of this dissertation, in the context of digital placebo effects, we explored whether efficacy expectancies could be successfully induced in a smartphone-based placebo mental health intervention. Efficacy expectancies decreased throughout intervention days, in all conditions, however least in the combined expectancy condition (prospective and retrospective expectancies were induced) and in the control condition, most in the prospective expectancy condition only and the retrospective expectancy only condition. These findings extend knowledge of previous studies investigating effects of different prospective efficacy expectancies on clinical outcomes in patients undergoing real-world heart surgery (Rief et al., 2017). Another study (Krzystanek et al., 2019) contributed to the field of digital placebo effects in a broader sense by investigating the efficacy of a smartphone-based telemedicine platform developed for patients with schizophrenia. An experimental group received the fully functional platform, a control group received a platform with limited functionality. After 12 months, depressive scores of patients had decreased in both the experimental and the control group, implying that the mere possession of the device may provide a psychological benefit. However, to our knowledge, we were the first ones who investigated the induction of efficacy expectancies as a potential factor underlying digital placebo effects in a particularly designed smartphone-based placebo mental health intervention. The findings provide experimental evidence in the context of previously conceptually discussed digital placebo effects (Gruszka et al., 2019; Tonning et al., 2019; Torous & Firth, 2016).

Taken together, in publication 1, there is evidence of the applicability of smartphone-based micro-interventions, based on psychotherapeutic techniques, evoking short-term mood changes. This response to smartphone-based psychotherapeutic micro-interventions may be increased by the application of an RF approach (publication 2). Publication 3 investigated efficacy expectancies as a potentially underlying mechanism of treatment response, such as, for instance, digital placebo effects.

Strengths and limitations of the findings

The studies included in this dissertation have several strengths. First, we delivered the smartphone-based psychotherapeutic micro-interventions (publications 1 and 2) and the smartphone-based placebo mental health intervention as well as efficacy expectancies (publication 3) in a standardized way through self-designed video clips and preprogrammed surveys on the smartphones and online. The option of full standardization represents a methodological advance of smartphone-based interventions, thereby reducing heterogeneity by different experimenters and protocols (Gruszka et al., 2019). At the same time, the studies allowed to meet the individual needs of participants by letting them select their preferred micro-intervention strategies (publication 1) as well as intervention times (publications 1 and 3). Second, in contrast to findings from previous eHealth trials (Baumel, Muench, Edan, & Kane, 2019; Eysenbach, 2005), there were high completion rates in both of the current studies with data available for over 90% of cases, which makes our findings relatively robust. Third, we used state-of-the-art statistical approaches. In publications 1 and 3, we applied mixed model analyses, which allowed to account for individual variations in mood respectively efficacy expectancies across intervention days and for missing data. In publication 2, we conducted a mixed effects RF algorithm accounting for the nested structure of the data, which was, at the time of drafting the publication one of the most recent advances in RF analyses (Bürgin & Ritschard, 2015). Fourth, the results have a high ecological validity, because participants used their own smartphones in a real-world setting at individually selected training times (publications 1 and 3) and in situations when they felt stressed (publication 3). Fifth, in both studies included in this dissertation, we provided micro-interventions and the placebo mental health intervention as short video clips designed by our group as well as by adapting the open-source *ohmage* app (Hicks et al., 2011). These interventions can be provided at minimal costs, enabling their utilization in low- and middle-income countries.

The findings of these studies need to be interpreted in lights of several limitations. First, the study samples were rather homogenous. In publications 1 and 2, all participants were male, of Korean nationality, and experienced with smartphones, whereas in publication 3, most of the participants were female psychology students. In both studies, healthy participants were included, thus, the findings may be generalizable rather to prevention-seeking populations. Future studies should also focus on clinical samples. Second, with a total duration of 13-days of ambulatory smartphone-based micro-interventions and without follow-up (publication 1), it is not possible to draw conclusions on the long-term stability of changes in mood, the latter being questioned in a previous study (Elefant et al., 2017). Third, the study which publications 1 and 2 are based on, did not include a control condition for the smartphone-based micro-interventions, thus, no assumptions on causality of the mood changes can be made, which may be, for instance, caused by digital placebo effects. Therefore, it is highly relevant to investigate potential underlying mechanisms of change of smartphone-based mental health interventions which we addressed in publication 3 in a classical RCT and found that efficacy expectancies should be considered in digital mental health research. Future studies should explore whether different efficacy expectancies affect behavioral outcomes such as mood (Stalujanis et al., in preparation). Furthermore, the interplay between digital placebo effects and placebo effects occurring in a face-to-face setting (Gaab, Kossowsky, Ehlert, & Locher, 2019) remains an open question, which may be relevant for blended psychotherapeutic treatment approaches, gaining even more importance in the course of the COVID-19 pandemic (Kooistra et al., 2019; Wind et al., 2020).

Implications of the findings

The findings of the publications included in this dissertation may have several implications. Publication 1 provides evidence of the applicability of psychotherapeutic smartphone-based interventions to elicit mood changes in a real-world setting. Thus, micro-interventions may be a promising low-barrier and non-stigmatizing approach to psychotherapeutic treatment for populations with relatively low motivation and engagement for classical face-to-face psychotherapy (Baumel et al., 2020). Future studies should further explore the efficacy of different types of smartphone-based micro-interventions which are currently mostly based on CBT techniques, and address different study populations, particularly those with limited access to conventional psychotherapy. In line with the precision medicine approach (F. S. Collins & Varmus, 2015), it has been suggested to integrate single micro-interventions as part of a larger treatment plan, under the umbrella of concepts such as the Behavioral Intervention Technology (BIT) model (Mohr, Schueller, Montague, Burns, & Rashidi, 2014) or "digital micro intervention care" (Baumel et al., 2020). Such a scalable and adaptive approach may be useful for prevention and treatment of mental disorders to avoid both under- and overtreatment (Stalujanis, Meinlschmidt, Belardi, & Tegethoff, 2020). Even though the smartphone-based micro-interventions described in the publications 1 and 2 were well tolerated and had high completion rates, they were rather conventionally designed. To address the usually low engagement rates in eHealth trials (Eysenbach, 2005), Graham and colleagues (2019) suggested a more user centered design for experimental therapeutics, which may, for instance, include game-like interventions (Fleming et al., 2017).

To tailor treatment to an individual, information is required on the timing when a certain intervention may be effective for a specific individual (Nahum-Shani et al., 2018). In this regard, publication 2 provides first evidence of the applicability of an RF ML approach to predict treatment response to psychotherapeutic micro-interventions, based on mood changes from the previous intervention day and from the intervention day. To avoid overfitting, only a limited number of predictors was included. Thus, future studies should be conducted in larger samples and include multisource information, such as situational and contextual information, psychological measures, and ambulatory biomarkers (Meuret et al., 2015). As publication 2 was the first study in this field, there are many open research questions to address, for instance, the applicability of ML to predict treatment response of smartphone-based interventions in different populations, validating whether other ML approaches than RF models may be better suited for prediction, and whether the approach applied in publication 2 may be useful for differential therapy indication.

The findings from publication 3 have been acquired in a classical RCT, which is required to make causal assumptions regarding the efficacy of a treatment. However, to address the gap between technology development, research, and clinical implementation, alternative research designs such as micro-randomized trials have been suggested (Bidargaddi, Schrader, Klasnja, Licinio, & Murphy, 2020). Findings from this dissertation suggest that to enhance the field of personalized medicine, different methodological approaches need to engage with each other. For instance, publication 3 provides evidence of potentially underlying mechanisms in smartphone-based mental health interventions, such as the micro-interventions delivered in publication 1, from a classical RCT. Findings from publication 2 suggest that to shed light on the question when placebo effects may occur, future studies should investigate predictors of efficacy expectancies on an intra- and interindividual level to design customized interventions.

Conclusion

The aim of this dissertation was to further scrutinize the utilization of smartphone-based interventions to improve mental health. The findings suggest that smartphone-based micro-interventions, based on psychotherapeutic techniques, may be a promising tool to elicit mood changes in real-world settings. Furthermore, evidence is provided of the applicability of an ML-based RF algorithm for the prediction of treatment response to psychotherapeutic micro-interventions eliciting mood changes. Additionally, this dissertation includes the first empirical study investigating whether efficacy expectancies could be successfully induced in a smartphone-based placebo mental health intervention. In line with the precision medicine approach, the findings may pave the way for future endeavors to provide personalized digital mental health treatment, and thus, to further promote the promising fields of eHealth and mHealth.

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