Evaluating the effectiveness of innovative psychological intervention tools in optimizing health outcomes: A multimethod approach

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General discussion

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In the present thesis, we aimed to examine the effectiveness of innovative psychological interventions on health outcomes by (1) evaluating the effectiveness of innovative psychological tools, i.e., serious gaming, verbal suggestions, and internet-based interventions, on various health behaviors and psychophysiological outcomes; (2) providing a concise overview of the current existing evidence of psychological interventions in optimizing immune function in response to *in vitro* or *in vivo* immunological as well as psychophysiological challenges; and (3) incorporating various self-reporting, behavioral and psychophysiological outcome measures both at baseline and in response to *in vitro* or *in vivo* immunological as well as psychophysiological challenges, including psychophysiological, physical and/or cognitive stressors, to concisely evaluate the effectiveness of psychological interventions on health outcomes. In this final chapter, we will discuss the findings resulting from the work described in this thesis. We also discuss the findings in light of their possible limitations and highlight potential implications for future research and clinical practice.

Evaluating the effectiveness of innovative psychological tools

Serious gaming to optimize health behaviors

As a first objective, we investigated the effectiveness of innovative psychological tools on health outcomes. A promising innovative psychological tool is serious gaming, as previous literature provided support for the effectiveness of serious gaming in optimizing health outcomes (28, 29). Serious games aim to alter health behaviors by optimizing targets, including self-efficacy, knowledge and skills in an entertaining manner (335). However, a meta-analysis of Desmet and colleagues (2014) showed that the effects of serious gaming varied along the incorporated outcome measures and were most conclusive for the determinants of behavior change, including knowledge and intentions to change behaviors, instead of changing actual health behaviors. The varying effects might be at least partially due to the fact that behavioral evaluations were less often incorporated and high heterogeneity was observed between studies in the incorporated outcome measures. Therefore, in Chapters 2 and 3, we evaluated the effectiveness of serious gaming on self-reported and observed behavioral outcomes in the domains of food and physical activity to receive more insights in the steps underlying health behavior changes. In Chapter 2, we focused on optimizing food outcomes and physical activity by providing participants with several health-related games during one session. These games were based on various serious components, i.e., transferring knowledge, priming and evaluative conditioning, combined with entertaining components, including providing participants with feedback and rewards. In Chapter 3, we specifically focused on optimizing food outcomes by health-related games based on approach and avoidance

training during one session. These games were accompanied or not with verbal suggestions and yielded the same entertaining components as applied in the serious games of Chapter 2. In Chapters 2 and 3, we found comparable results in that the serious gaming session affected predictors of health behaviors but did not affect behavioral outcomes. The results of Chapters 2 and 3 therefore seem restricted to optimized intentions and attitudes rather than actually implemented health behaviors. However, as serious gaming is a rather innovative tool and these studies did mostly incorporate evaluations of predictors of health behaviors rather than evaluations of behavior change (28), there is no conclusive view yet on the components of serious gaming that are effectively resulting in behavioral changes. Serious games can for example vary in the incorporation of serious and entertaining components, as well as in the intensity in which they are provided. Possibly, optimization of these serious gaming components can minimize the gap between intentions and behaviors.

Serious and entertaining components of the serious games

The serious components that were incorporated in the serious games of Chapters 2 and 3 all comprised strategies that were based on behavioral learning principles (68, 105, 336). It can be hypothesized that combining multiple behavioral learning principles would be more beneficial compared to incorporating only a single behavioral learning principle, as it provides the opportunity to tap into multiple learning processes. The meta-analysis of Desmet and colleagues (2014) found that multicomponent games showed higher effect sizes compared to standalone games, but both kind of games showed significant effects on health-related outcomes (28). One recent study also combined multiple behavior change strategies targeting various learning processes to improve snacking behaviors in adolescents using a mobile application, but did not find support for the effectiveness of the intervention (337). Although Chapter 2 was based on multiple behavioral therapeutic learning principles that target various learning processes, including transferring knowledge, priming and approach avoidance training, and Chapter 3 focused specifically on approach avoidance training, both Chapters yielded comparable results. Therefore, no support could be found for the add-on effectiveness of combining multiple strategies. However, as the results so far are heterogeneous and as both Chapters 2 and 3 are proof-of-concept studies, more research is needed on whether combining various evidence-based strategies can strengthen the effectiveness of serious gaming.

Besides the serious components, we incorporated various entertaining components into the serious games. In both Chapters 2 and 3, we included rewards, e.g., by providing participants with trophies and points, and provided the participants with feedback on performance, to enhance engagement with playing the games. Although we did not

incorporate formal evaluations of engagement in our study designs, participants reported that the games were rather enjoyable to play, and we did not find any indications that the games were not engaging. In e-health studies, providing rewards and feedback are most frequently incorporated as incentives to enhance engagement (139). Although literature on the effective entertaining components in serious games is not yet unequivocal, previous studies have pointed out that an optimal blending of the serious components and the entertaining components is essential for the effectiveness of serious games (28). It can be suggested that tailoring the serious games to the specific needs of the individual is needed to provide an optimal personalized blending of the serious gaming components. Previous reviews provided support for optimizing the effectiveness of serious games by tailoring the components to the individual (28, 139).

Intensity of the serious games

It can be suggested that serious gaming during one single session, as in our experiments, can alter precursors of health behaviors, but is not sufficient to alter health behaviors. However, no consensus in the literature exists on the ideal serious gaming duration and frequency. Whereas the average study duration was 4 hours in one meta-analysis (28), and 9 weeks in another (58), both meta-analyses failed to find support for a longer gameplay duration being more effective (28, 58). In contrast to interventions with a longer duration, shorter interventions provide opportunities to reduce time and costs of interventions. Furthermore, no guidelines exist regarding the minimal duration of interventions in order to induce optimized health outcomes. A study analyzing the minimal intervention intensity to optimize health outcomes showed that increasing the intensity of interventions is not always necessary to increase their effectiveness, as interventions with low intensity can also be effective in producing health behavior changes (338). The effects of behavior change interventions, however, were stronger when follow-up guidance was added to the intervention (338). Therefore, future research should investigate whether optimization of health behaviors can be realized when offering personalized guidance according to the specific individual's needs. Guidance can be provided through an online environment in which written guidance feedback is given in response to homework assignments and questions of the participant, as was done in Chapters 6 and 7 in which serious gaming was combined with internet-based cognitive behavioral therapy (CBT). Furthermore, participants can be provided with face-to-face or telephonic follow-up contact focusing on maintaining goals and relapse prevention, as was also done in Chapters 6 and 7.

Alternatively, there exists no consensus for the ideal gameplay absolute intensity and duration, since this may significantly depend on the preexisting knowledge and skills as well as the needs of the individual. It would be interesting to investigate in future research

whether it is effective to tailor the gameplay intensity and duration, as well as the way and intensity in which guidance is provided according to the needs of the individual. This can for example be done by adjusting the guidance according to the individual's goals and needs regarding health behavior optimization.

Optimizing outcome expectancies to enhance the effectiveness of psychological interventions

Another innovative tool that can be implemented into psychological interventions concerns optimizing outcome expectancies, as placebo research on optimizing outcome expectancies showed that verbal suggestions can improve health outcomes (13). There are various ways through which outcome expectancies can be optimized, including instructional learning, conditioning and observational learning (152). In Chapters 3 and 4, we aimed to optimize outcome expectancies through instructional learning by providing participants with verbal suggestions. In Chapter 3, we provided participants with verbal suggestions concerning the effectiveness of serious gaming next to completing the serious games. The findings provided some preliminary support for the add-on effectiveness of verbal suggestions onto serious gaming based on approach-avoidance strategies. As we only found limited support for this add-on effectiveness of the verbal suggestions and not for the verbal suggestion on its own, the results in Chapter 3 are in line with previous research, demonstrating that a combination of techniques, such as for example conditioning and verbal suggestions, is more effective compared to the standalone interventions (339, 340). However, we did not find any support for the add-on effectiveness of verbal suggestions in Chapter 4, in which participants were provided with verbal suggestions concerning the effectiveness of a relaxation practice next to actually performing the relaxation practice. As the results of the proof-of-concept studies described in Chapters 3 and 4 are not conclusive regarding the effectiveness of verbal suggestions in optimizing psychological intervention effects, more research on this topic is needed. It can be presumed that the content of verbal suggestions as well as the frequency in which verbal suggestions are provided to participants are key components that contribute to the effectiveness of verbal suggestions (152, 341).

Content of the verbal suggestions

The verbal suggestions that were applied in Chapter 3 were based on a combination of optimizing outcome expectancies and optimizing contingencies between the stimulus and response, i.e., influencing actions of approaching and avoiding without actually performing these actions (342, 343). In Chapter 4, the verbal suggestions were also based on optimizing outcome expectancies and contained instructions on how to perform a

relaxation practice. Both the verbal suggestions of Chapters 3 and 4 therefore covered the key components of the intervention. Previous studies showed that providing people merely with verbal instructions concerning stimulus-response contingencies without actually performing a training is effective in optimizing approach avoidance effects (342). However, this is not yet confirmed for relaxation instructions and we did not find any support for the effectiveness of the verbal suggestions in Chapter 4. Future studies should therefore further elucidate whether the add-on effectiveness of verbal suggestions can be generalized to various psychological intervention strategies or seems restricted to certain concepts. Although beyond the scope of the proof-of-concept studies of Chapter 3 and 4, it can be presumed that the effective content of verbal suggestions varies along individuals. Prior literature pointed out that there are substantial individual differences in placebo responses (344, 345), for instance due to differences in prior experiences (346). It would therefore be interesting to examine whether providing verbal suggestions that are specifically tailored to the individuals' needs can optimize the effectiveness of the suggestions.

Booster suggestions

As learning processes can be strengthened by repeatedly presenting an individual with the same stimulus (347), increasing the frequency of providing the verbal suggestions could possibly strengthen the effectiveness of the verbal suggestions. In Chapter 3, the verbal suggestions were repeated after each of the outcome measures, whereas the verbal suggestions in Chapter 4 were only presented once. A study of Colloca and colleagues (2010) showed that the number of conditioning trials affected the strength of the analgesic responses, in that a higher number of conditioning trials resulted in increased analgesic effects (348). Although this relation between the frequency of providing verbal suggestions and its subsequent effectiveness is not yet clear yet for verbal suggestions, it could be hypothesized that the differences in the frequency with which the verbal suggestions were presented in Chapters 3 and 4 might have affected the differential findings. It would therefore be interesting to investigate whether increasing the number of (booster) suggestions could strengthen the instructional learning effects in the context of psychological intervention strategies.

Optimizing health outcomes by combining an internet-based intervention with serious gaming

In Chapter 6, we provided the study protocol for evaluating the effectiveness of a six-week guided internet-based CBT intervention accompanied with serious gaming elements in healthy participants. We evaluated the effectiveness of this intervention in Chapter 7 by

incorporating various immunological and psychophysiological challenges, including a BCG-vaccine, and found no significant effects for optimized outcomes on our primary outcome, vitality. However, we found effects on related constructs, in that bodily sensations (including head ache, nausea and other types of sensations that are usually experienced as being annoying) and sleep problems decreased after the intervention. In addition, self-reported well-being decreased less after the test day with psychophysiological challenges, including psychophysiological, physical and/or cognitive stressors, in the intervention condition compared to the control condition. Furthermore, we found some limited support for differential effects on circulating blood chemokines at the end of the test day, as well as for increased IgG antibody levels four weeks after a BCG-vaccination. In addition, it is known that internet-based interventions in general have high drop-out rates, of around 20% (349, 350). However, for our internet-based CBT intervention in Chapter 7, only 3 out of 35 participants (8.6%) discontinued with the intervention, providing support for the effectiveness of our intervention in keeping participants engaged with the intervention. Therefore, a combination of guided internet-based CBT and serious gaming for six weeks provides promising results in optimizing health outcomes.

Possible effective intervention components

Chapter 7 did not only show optimized self-reported outcomes at rest, but also optimized self-reported well-being in response to psychophysiological challenges and limited support for differential chemokine responses and increased IgG antibody levels four weeks after a BCG-vaccination, whereas the results of Chapters 2 – 4 were mainly limited to self-reported outcomes. There are several factors that may have contributed to these findings. First of all, Chapter 7 focused on a combination of internet-based CBT and serious gaming during six weeks, whereas Chapters 2 – 4 were focused on serious gaming or relaxation, respectively, during one single session. It can therefore be hypothesized the combination of multiple innovative intervention tools and the duration have affected the effectiveness of the psychological interventions. Furthermore, the intervention in Chapter 7 was guided by a therapist and tailored to the specific needs of the participant. As the interventions in Chapters 2 – 4 were unguided and not tailored to the specific needs of the individual, this might have led to the less conclusive results compared to Chapter 7. Finally, the results of Chapter 7 were not only measured directly after the intervention as was done in Chapters 2 – 4, but also four weeks afterwards. Moreover, we incorporated a booster session two weeks after the intervention in Chapter 7 to focus on relapse prevention. It can be hypothesized that participants need time to optimize health outcomes and by combining this time with a booster session focusing on relapse prevention contributed to the findings on immune outcomes after a BCG-vaccination.

Although the combination of internet-based CBT and serious gaming already yielded promising results in Chapter 7, it would be interesting to optimize the serious gaming sessions by tailoring the intensity and duration according to the individual needs and by implementing elements of augmented reality. In addition, we did not apply verbal suggestions in Chapter 7. Since Chapter 3 provided some support for the add-on effectiveness of verbal suggestions onto serious gaming, future studies could evaluate whether adding verbal suggestions onto internet-based CBT with serious gaming elements can further optimize these effects. Finally, the usability of the intervention can be further optimized, as the serious games that were provided were only available in a computerized version. It would be interesting to combine the serious game and the internet-based CBT intervention in one mobile application to be able to remind participants with mobile notifications of their homework assignments and to make the intervention even more accessible.

Providing an overview of the evidence of psychological interventions in optimizing immune function

Next to the innovative intervention tools for optimizing health outcomes including immune function, we aimed to provide a concise overview of the currently existing evidence for psychological interventions in optimizing immune function. We therefore investigated the effectiveness of psychological interventions in optimizing immune function by a meta-analytic review in Chapter 5. A previous meta-analytic review did not allow conclusive statements on the effectiveness of psychological interventions on immune function due to substantial heterogeneity in study designs and incorporated outcome measures that were usually assessed during resting states (169). We therefore hypothesized that confronting participants with a challenge, i.e., a stimulus that provokes an immune system response like a vaccine, provides more insights in the actual responsiveness of the immune system to a natural challenge. We performed a meta-analytic review focusing on studies that incorporated an *in vitro, in vivo* or a psychophysiological challenge into the study design. Overall, we found support for a small to moderate effect of psychological interventions on optimizing immune function, although large heterogeneity was observed in the incorporated study population, psychological interventions and immune outcome measures. Moderate effects were found when studies incorporated *in vivo* immunological challenges to evaluate the effectiveness of psychological interventions, while small effect sizes were found for *in vitro* challenges and no significant effects were found for psychophysiological challenges.

In vivo immunological challenges

As highest effect sizes on immune outcomes were found for studies incorporating *in vivo* challenges, such challenges are rather promising to incorporate in future research. Although the results from studies incorporating *in vitro* and psychophysiological challenges provide rather insightful information in the immune response compared to e.g., counting cells in resting states, those challenges presumably yield a more complex interpretation compared to *in vivo* immunological challenges (e.g., faster wound healing). Since *in vitro* immunological challenges are provided outside the body after sample manipulation, they are likely to be more distantly associated with the subtle behavioral responses and thus may confound their detection. Furthermore, it is not known whether psychophysiological challenges yield a direct causal relation with the immune outcome. We therefore hypothesized that incorporating *in vivo* immunological challenges that are carefully matched to the incorporated study population would provide most promising opportunities to evaluate the effectiveness of psychological interventions on immune function directly *ex vivo*. For example, a study of Witt (2003) included patients with birch pollen allergy and challenged them with a histamine provocation test after receiving a psychological intervention or being allocated to the control condition, receiving no intervention (301). They found a differential immune response in participants that received the intervention as compared to the participants that did not receive any intervention. As the results of this study do not only provide insights in that a psychological intervention can alter immune function, but also specifically in how a psychological intervention can result in less symptoms for a certain condition, it provides insights to what extent a psychological intervention can possibly support regular treatments for a specific condition, in this case birch pollen allergy.

In vitro and psychophysiological challenges

As described above, the interpretation of the outcomes derived from *in vitro* and psychophysiological challenges is somewhat more complex compared to the interpretation of the outcomes of *in vivo* immunological challenges. However, *in vitro* and psychophysiological challenges can provide additional insights into immune responsiveness with respect to *in vivo* immunological challenges, as they challenge specific immune cells in a different way. Therefore, *in vitro* and psychophysiological challenges might be suitable add-on challenges onto *in vivo* challenges. Future studies on the effectiveness of psychological interventions on immune outcomes might more consistently incorporate various combinations of challenges in various somatic conditions to gather more insights in the immune response after a psychological intervention. The combination of challenges that should be incorporated in a study depends on the included study population as well as

on the aims of the intervention. For instance, when an intervention is specifically focused on optimizing coping with stress, it would be interesting to incorporate a social evaluative stressor into the study design accompanied with an *in vivo* immunological challenge, such as a Hepatitis B vaccine, as stress can suppress Hepatitis B antibody responses (351). Furthermore, future studies should take the order into account in which they expose participants to specific challenges. It can for instance be presumed that more insights in immune functioning are gathered when the *in vitro* immunological challenge is not only provided prior to the *in vivo* or psychophysiological immunological challenge, but also afterwards. By performing the *in vitro* immunological challenge before and after another challenge, it would be possible to gain more insights in immune function in response to various gradations of challenges.

Incorporating various outcome measures and challenges to evaluate the effectiveness of a psychological intervention on health outcomes

As outlined above, it would be interesting to observe the immune response to a combination of multiple *in vitro* and *in vivo* immunological as well as possibly psychophysiological challenges in order to gather more insights in the underlying mechanisms of the immune response. In Chapters 6 and 7, we therefore explored the effectiveness of a psychological intervention on health outcomes in healthy participants by exposing them to a combination of *in vitro* (i.e., LPS stimulation) and *in vivo* (i.e., BCG-vaccination) immunological as well as psychophysiological challenges (i.e., PASAT, CPT and TSST). When looking at the basal psychophysiological outcomes and the self-reported and psychophysiological outcomes in response to the challenges, some preliminary indications were found for differential outcomes on the physiological outcomes of heart rate. However, no significant effects were found for cortisol and alpha amylase, as measured in saliva. In response to the psychophysiological challenges on the test day, we found higher levels of self-reported well-being after the intervention compared to the control condition. Furthermore, we found some support for increased IgG antibody responses four weeks after the BCG-vaccination in the intervention condition compared to the control condition. In addition, there was some preliminary support for differential effects on immune outcomes after the test day in the intervention condition versus the control condition. These differential immune response patterns were only visible in the context of the challenges, i.e., the *in vitro*, *in vivo* immunological and/or psychophysiological challenges. This is in line with the hypothesis that a combination of challenges is needed to be able to activate a differential immune response pattern. As we incorporated healthy participants, floor effects can be observed likely due to the fact that they already possess an adequate immune system. Therefore, it can be presumed that the challenges are necessary to

uncover potentially differential health outcomes. To provide more insights in the clinical relevance of a psychological intervention on health outcomes, the findings of Chapter 7 should be replicated in persons that are at increased risk of health problems due to immune disorders.

Evaluating health outcomes with various outcome measures

In the studies that were performed in the present thesis, various self-reporting (Chapters 2 – 4, 7), behavioral (Chapters 2 and 3) and psychophysiological (Chapters 4 and 7) outcome measures both at baseline and in response to *in vitro* or *in vivo* immunological (Chapter 7) as well as psychophysiological challenges (Chapters 4 and 7) were included to assess health outcomes. In Chapter 7, we included an *in vivo* challenge of the immune system by providing participants with a live-attenuated BCG-vaccination and found some support for increased IgG antibody levels after the intervention. As antibody responses to the live-attenuated (replicating) BCG vaccine approximate the physiological response to a natural infection, these findings provide limited support for the effectiveness of the psychological intervention of Chapter 7. However, this study was the first incorporating a BCG-vaccination into a study design evaluating the effectiveness of a psychological intervention and as the present findings were not yet conclusive, they should be confirmed and extended by future research. In Chapter 7, the most conclusive findings came from self-reported outcomes, whereas psychophysiological and immune outcomes yielded less conclusive findings. This discrepancy was also observed in Chapters 2 – 4, in which the results were more conclusive for self-reporting outcomes, whereas no significant effects were found for behavioral or psychophysiological outcomes. Studies that evaluate the effectiveness of psychological interventions on health outcomes often rely on self-reported outcomes (28, 352-354), while results on behavioral and psychophysiological outcomes are in general less conclusive. As the primary outcome in Chapters 2, 3, 4, and 7 was based on self-report, the sample size was powered accordingly. Possibly, the studies may therefore not have been sufficiently powered to detect significant differences for the other behavioral and psychophysiological outcomes. Therefore, Chapters 2, 3, 4, and 7 provide a first step in evaluating health outcomes with multiple methods. Future studies should more consistently incorporate behavioral and psychophysiological outcomes next to self-reported outcomes to gather more insights in the underlying mechanisms of health outcome optimization. Moreover, although we observed health behaviors in Chapter 2 and 3, we did not incorporate observations of health behaviors in Chapter 7. Future research should also systematically incorporate observations of health behaviors, including physical activity and eating behaviors. These data can be collected through wearable devices that can detect both energy intake and expenditure (355).

Strengths and limitations

The present thesis has multiple strengths that are worth mentioning. First of all, the present thesis incorporated various innovative psychological intervention tools to optimize health outcomes. By incorporating tools, including serious gaming, verbal suggestions, and internet-based CBT, separately but also combined, more insights were gathered in how to optimize the effectiveness of existing psychological interventions. Second, we incorporated various self-reported, behavioral and psychophysiological outcome measures to evaluate the effectiveness of those tools. In addition, we incorporated various physical and psychophysiological challenges, including a BCG-vaccination to gather more insights in the processes underlying health optimization. As we are aware that multiple testing increases the risk of type 1 errors, we adjusted the relevant p-values accordingly. Therefore, the present thesis was able to gather a multi-perspective view on the effectiveness of innovative psychological interventions on health outcomes.

Next to the above-mentioned strengths of the work presented in this thesis, there are also some limitations that should be mentioned. First of all, the effect sizes that were found in the studies from Chapters 2, 3, 4, and 7 were variable and statistically small. This can at least partially be due to the fact that the experimental studies in these Chapters all entailed proof-of-concept studies in healthy subjects with innovative intervention components and outcome measures. As the included interventions in Chapters 2, 3, 4, and 7 provide a first step towards health optimization, future studies should be carried out to further confirm the present findings. Second, in the experimental studies of Chapters 2, 3, 4, and 7, only healthy participants between 18 and 35 years of age were included. We incorporated a rather homogeneous population in our studies to exclude as many alternative explanations for the conclusions as possible, and to explore whether health outcomes can be further optimized in a healthy population, i.e., primary prevention. The next step would be to investigate whether the interventions can also serve as secondary or tertiary prevention tools. Therefore, the results of our experimental studies should be replicated in populations at risk for health problems or those suffering from chronic diseases. Third, although we do not have indications that the verbal suggestions in Chapters 3 and 4 were not credible to participants, future studies should include manipulation checks to assess the credibility of the verbal suggestions used. Finally, although we aimed to enhance engagement within the studies that included serious gaming elements, i.e., Chapters 2, 3, and 7, we did not evaluate whether engagement with the serious games or with the psychological CBT intervention was actually optimized by playing the games. Therefore, future studies should develop valid assessments of engagement in order to evaluate it more structurally when including serious gaming elements into the study design. Finally, in order to strengthen the theoretical basis of the psychological interventions that we

incorporated in Chapters 2, 3, 4 and 7, we combined multiple techniques and methods into the interventions. However, we were not able to disentangle and examine the effectiveness of the included components in these interventions.

Future research directions

The present thesis extends current knowledge on the effectiveness of innovative psychological intervention tools in optimizing health outcomes by incorporating various evaluation methods, and provides several promising opportunities for future research.
First, the studies performed in Chapters 2 – 4, 6 and 7 are all performed in a rather homogeneous and healthy student sample, which limits the generalizability of the findings. Therefore, the studies should be replicated in patients at increased risk of health problems, including patients with somatic conditions and possibly immune disorders, in order to see whether the interventions can be effective tools for secondary and/or tertiary prevention. More specifically, the serious games that were incorporated in Chapters 2 and 3 should also be provided to populations at risk for health problems due to an unhealthy lifestyle, e.g., people with obesity or metabolic syndrome. In addition, the relaxation practice that was implemented in Chapter 4 should be applied to a population with (sub) clinical levels of experienced stress, to see whether it is actually effective in reducing stress in a population at risk for health problems due to stress. Finally, the internet-based CBT intervention along with the serious game that was incorporated in Chapters 6 and 7 to optimize health outcomes can also be investigated in patients with somatic conditions. As the intervention was effective in optimizing bodily sensations and sleep problems, it would be interesting to apply this intervention to a population where these factors play a major role in the maintenance and/or deterioration of the somatic condition, including for example patients with medically unexplained symptoms such as fibromyalgia (356), but also patients with other somatic and psychological conditions.

Second, future studies concerning serious games should focus on creating an optimal blending of the serious components and the entertaining components in serious games. Therefore, future studies might aim to make rewards in serious games more meaningful for everyday life. This could be realized by adding elements of augmented reality into serious gaming, i.e., applying the serious game in the real world to enhance engagement (357). In the context of optimizing health outcomes, serious games could for example include realistic rewards when people show optimized health behaviors (e.g., discounts on healthy food products and/or subscription to a fitness center) and they could include tailored feedback on how to optimize their health behaviors according to the health goals and values of the individual (358). It can be hypothesized that when features of

augmented reality are added onto the serious games, the gap between intentions and behaviors can be bridged, as users are able to directly apply the acquired knowledge and skills in their daily lives.

Third, we only included verbal suggestions in the context of serious gaming and relaxation interventions. Future studies should also investigate the add-on effectiveness of verbal suggestions to other psychotherapeutic interventions. As described above, it would be interesting to tailor the verbal suggestions onto the specific individual needs, and if booster sessions turn out to strengthen the effectiveness of verbal suggestions, the number of booster sessions could also be individually tailored. Besides, although the present thesis was based on optimizing outcome expectancies through instructional learning, placebo literature supported that outcome expectancies can also be enhanced by observational learning, i.e., observing behavior of another individual (i.e., a demonstrator) to gather more insights in a situation and possible reinforcing consequences of certain behaviors and subsequently to create a change in the behavioral patterns of the observer (152, 339, 359, 360). For example, observational learning has shown to be effective in increasing analgesia (152, 361). A study of Colloca and Benedetti (2009) showed that social observation of a demonstrator who underwent the whole experiment resulted in increased levels of placebo analgesia in the observer when they underwent the experiment themselves (361). Observational learning based on social observation could specifically be interesting in the context of a psychophysiological challenge (e.g., TSST), as was implemented in Chapter 4. Possibly, participants feel more efficacious in coping with the stressor after observing a demonstrator undergoing a social evaluative stressor prior to being exposed to the task by themselves. Finally, the present thesis aimed to optimize psychological intervention tools by combining various intervention components. In Chapters 2 and 3, we included various serious and entertaining components into the serious games. In Chapters 6 and 7, serious gaming components were supplemented to internet-based CBT to optimize the effectiveness of the psychological intervention. As the studies in Chapters 2, 3, 6 and 7 were proof-of-concept studies and performed to evaluate the effectiveness of the psychological intervention as a whole, we were not able to disentangle the effectiveness of the individual techniques and components that were incorporated. Therefore, future research should further investigate the effectiveness of the individual components, as well as the most optimal combination of these components in order to enhance the effectiveness of the psychological intervention. Future studies could for example evaluate whether the combination of multiple components, e.g., various relaxation practices, is more effective than incorporating a single component, e.g., one single relaxation practice, by comparing these interventions on their effectiveness in optimizing health outcomes.

Implications for clinical practice

The results of the present thesis suggest that the incorporated innovative psychological tools can, at least partially, be effective in optimizing health outcomes, which provides promising steps towards clinical practice. Below, we further elaborate on the implications for clinical practice and provide suggestions for future research that can provide further insights to bridge the gap between scientific research and clinical practice.
In Chapters 2 and 3, we investigated the effectiveness of serious gaming in optimizing food outcomes and physical activity. The serious games were effective in optimizing precursors of healthy food outcomes. Therefore, it would be interesting to further optimize the effectiveness of these games, i.e., by providing support through face-to-face contact or by telephone, and take further steps to implement them in primary health prevention programs. In addition, as serious games are known to optimize motivation to complete an intervention (26), serious games presumably are a rather promising add-on tool in existing psychological interventions.

In Chapter 3, we found some preliminary indications that verbal suggestions might be an effective add-on tool onto serious gaming. Although the add-on effectiveness of verbal suggestions was not confirmed by the results in Chapter 4, manipulating outcome expectancies presumably affects the effectiveness of the intervention (152). Future studies should therefore further investigate the effectiveness of verbal suggestions as an add-on tool to psychological interventions. When future studies demonstrate that verbal suggestions are an effective add-on tool to psychological interventions, this can have widespread implications for clinical practice. More specifically, healthcare professionals then should receive standardized education and training regarding the communication with the patient in order to minimize nocebo effects and to optimize placebo effects in clinical practice (344). When applying the verbal suggestions in clinical practice, it would presumably be best from an ethical perspective to yield an open-label approach instead of an hidden approach when providing patients with the verbal suggestions in clinical practice (362).

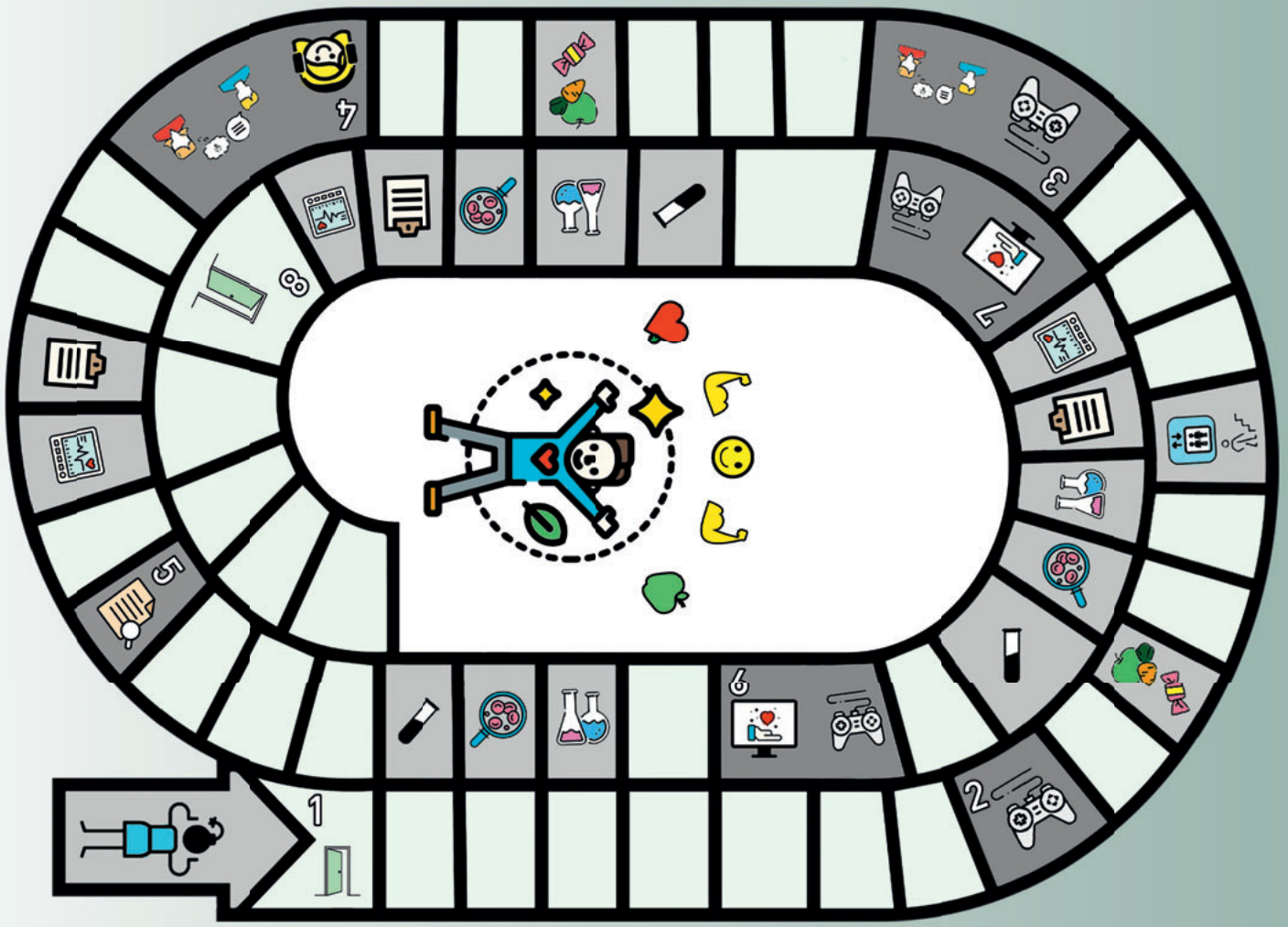
Furthermore, in Chapter 5, we found most conclusive effects for the effectiveness of psychological interventions on immune function when studies incorporated *in vivo* immunological challenges. When evaluating the effectiveness of a psychological intervention by incorporating live BCG-vaccination in Chapter 7, we found differential effects in IgG antibody levels in the intervention condition compared to the control condition, suggesting that the psychological intervention was effective in altering immune function. Previous literature also showed that psychological interventions can be effective in altering immune function when facing an *in vivo* immunological challenge: a

psychological intervention, for instance, showed to be effective in optimizing outcome of the allergic response to birch pollen (301), as well as optimizing wound healing in surgical patients (363). Therefore, it would be interesting for clinical practice to further investigate whether psychological interventions can supplement, or at least partially replace, current drug treatments in various somatic conditions to reduce side effects.
Finally, we found in Chapters 6 and 7 that multiple health outcomes can be optimized by the combination of internet-based CBT and serious gaming. Therefore, it would be interesting to provide patients with the option for internet-based CBT interventions next to regular face-to-face CBT interventions to tailor the way of providing the intervention to the specific preferences of the individual patient. Furthermore, it would be interesting to investigate whether serious gaming is an effective add-on tool towards internet-based CBT interventions. As stated above, the usability of the intervention can be optimized by providing the internet-based CBT intervention along with the serious game in one mobile application.

In summary, participants can benefit from innovative psychological intervention tools, including serious gaming, verbal suggestions, and internet-based interventions. Compared to traditional face-to-face interventions, innovative internet-based interventions can be timesaving, both for the patient but also for the therapist. However, in order to enhance its effectiveness, the effectiveness of tailoring the intervention specifically to the values and goals of the individual should be taken into account.

Conclusion

Taken together, the present thesis provides an overview of innovative psychological intervention tools aimed to optimize health and found preliminary support for the effectiveness of serious gaming, verbal suggestions and internet-based CBT on optimizing various self-reported, observational and psychophysiological measures of health. Evaluating the effectiveness of innovative psychological interventions on health outcomes by incorporating multiple psychophysiological methods and challenges provides more insights in the potential effectiveness of these interventions as well as in the mechanisms underlying health optimization.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