Official title of study:

A Personalized Approach to Effects of Affective Bias Modification on Symptom Change and Rumination

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1. *A personalized approach to effects of affective bias modification on symptom change and rumination. A randomized controlled trial.*

2. Introduction.

A main objective of this project is to investigate whether transdiagnostic rumination mediates the effects of affective bias modification on depressive symptoms. By combining general mechanisms research with a personalized symptom network approach, we will be in the forefront of understanding how a drug-free treatment option works and for whom it works best.

There is a growing consensus that the traditional approach to mental disorders in psychopathology research is constraining new scientific discoveries. Up until recently, research has been guided by the idea that a specific constellation of psychiatric symptoms reflects a specific psychiatric disorder, and that a specific pathogenic pathway causes this. However, findings based on this approach have not aligned with findings from clinical neuroscience and genetics, is poor in predicting treatment response, and does not seem to capture the underlying mechanisms of dysfunction (Insel et al., 2010). The problem is particularly disturbing for depression research, as depression is a very heterogenic disorder (Goldberg, 2011) with numerous plausible etiological and maintaining pathways (Charney & Manji, 2004; Wittenborn, Rahmandad, Rick, & Hosseinichimeh, 2016)and high levels of comorbidity (e.g., anxiety and alcohol use disorder; (Brown, Campbell, Lehman, Grisham, & Mancill, 2001; Kessler et al., 1997).

Rumination. There is growing evidence that rumination, a maladaptive form of self-reflection, might constitute a transdiagnostic factor. A particularly maladaptive sub-type of rumination, brooding, reflects the degree to which individuals passively focus on symptoms of distress and the meaning of those symptoms. Brooding is a vulnerability factor to Major Depressive Disorder (MDD) and it contributes to the development and maintenance of the disorder (Abela & Hankin, 2011; Sarin, Abela, & Auerbach, 2005). In bipolar disorder (BP), compared to MDD, ruminative responses are even more present (Kim, Yu, Lee, & Kim, 2012). Rumination predicts prospective changes in anxiety (Segerstrøm, Stanton, Alden, & Shortridge, 2003), as well as alcohol use in out-patients with a diagnosis of alcohol abuse, independent of depression and initial level of alcohol use (Caselli et al., 2010). Furthermore, brooding mediates the prospective relation between anxiety and depression (Grant et al., 2013). These associations suggest that rumination may play an important role across psychopathologies and contribute to the high rates of comorbidity among those disorders (Caselli et al., 2010; McLaughlin & Nolen-Hoeksema, 2011).

Affective bias. Affective biases, i.e. preferential attention to threatening information have been documented in subjects with clinical and subclinical levels of anxiety (Bar-Haim, Lamy, Pergamin, Bakermans-Kranenburg, & Van Ijzendoorn, 2007; Cisler & Koster, 2010). It has also been demonstrated that clinically depressed subjects, previously depressed subjects and never-depressed individuals at high risk because of family history, all display a bias towards sad faces (Gotlib, Krasnoperova, Yue, & Joormann, 2004; Joormann & Gotlib, 2007; Joormann, Talbot, & Gotlib, 2007). Studies indicate that the negative affective biases may constitute causative, vulnerability and maintenance factors for affective disorders, like depression and anxiety (Chan, Goodwin, & Harmer, 2007; MacLeod, Rutherford, Campbell, Ebsworthy, & Holker, 2002). However, although there have been quite a high number of studies examining affective biases in depression or anxiety individually, surprisingly few studies have examined affective biases among individuals with comorbid depression and anxiety (Gibb, McGeary, & Beevers, 2016).

Linking rumination, attentional control, symptoms and affective bias. Self-reports of rumination predict an affective bias towards negative stimuli, even when depressive symptoms are statistically controlled for (Donaldson, Lam, & Mathews, 2007). Negative biases are particularly strong in subjects with heightened disposition to engage in ruminative brooding (Joormann, 2006).

Rumination can be understood as dysregulated attentional focus on depression symptoms. Both trait and experimentally induced state rumination have been linked to impairment in executive control functions, in particular cognitive inhibition and switching (Joormann & Gotlib, 2010). This indicates that information-processing impairments might make it difficult for ruminators to disengage from negative content (Koster, De Lissnyder, Derakshan, & De Raedt, 2011).

The aforementioned findings have motivated an increase in interest in using knowledge about the mechanisms underlying the vulnerability and maintenance of affective disorders for therapeutic purposes (Harmer, Duman, & Cowen, 2017; Koster & Hoorelbeke, 2015). Given that one of the central mechanism in affective disorders is a selective attentional focus towards disorder-relevant stimuli, then reducing this focus could potentially alleviate the disorder. Computerized tasks that aim to induce changes to the bias in question have been developed (Hertel & Mathews, 2011). These procedures appears successful in reducing affective biases observed in depression, and might also lead to reductions in depression symptoms (Hallion & Ruscio, 2011).

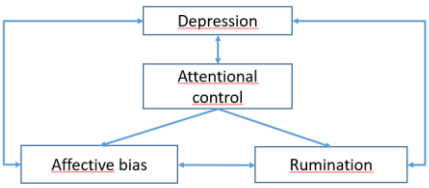

Figure 1. The relation between depression, attentional control, affective bias and rumination. Adapted from LeMoult & Gotlib (2018).

The symptom network approach. Given the above challenges, there has been a call for multi-level etiological models involving multiple causal processes at the micro and macro level, within and outside the individual (Kendler, Zachar, & Craver, 2011). The network approach offers a promising conceptual framework to explore the complex interplay between important psychopathological processes at the dimensional level (Hofmann, Curtiss, & McNally, 2016). By network analysis one can determine which symptoms are the most central (i.e., influential) based on the amount of influence that flows from one symptom to another (Borgatti, 2005). See figure 2. Networks with many strong connections between symptoms (dense networks) are more likely pathogenic than networks characterized by weaker connections (Borsboom, 2017). Simulation studies show that in dense networks, only a minimal of worsening in a central symptom may trigger a downstream cascade of symptoms. This might lead to a "vicious cycle" of negative cognition and symptoms (Wichers, 2014), with a depressed state as the result (Cramer et al., 2016).
Using intensive time series data on symptoms in combination with cutting-edge statistics, such as graphical vector autoregressive modelling, we can capture the within- and between-person temporal dynamics of individual symptom networks (Wild et al., 2010). Relevant psychological, physiological and behavioral variables can be gathered relatively easy by the use of smartphones (Miller, 2012). Analyzing such time-series data can reveal dynamic processes within each individual (Trull & Ebner-Priemer, 2009). In this manner, symptoms and other variables can be tracked over time to optimally model the continuous dynamics of the interplay between processes during improvement and worsening of a disorder, and before and after interventions. This approach can provide a more fine-grained examination of the dynamic interplay between depression-related processes at the individual level, and possibly help identify symptom profiles for which ABM might be effective. Thus, the network approach provides a potential framework for personalized assessment and treatment (Fried et al., 2017), and guide clinicians in choosing treatments that are tailor-made to address each patient's problem more effectively (Fisher, Reeves, Lawyer, Medaglia, & Rubel, 2017).

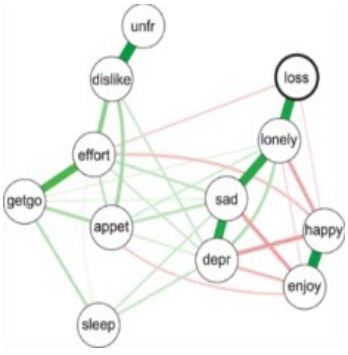

Figure 2. Example of a depression symptom network

Recently, researchers have advocated for the inclusion of non-symptom variables that are assumed to be plausible causal candidates in the etiology or maintenance of disorders (Jones, Heeren, & McNally, 2017). Rumination and affective bias are relevant variables that can be included in network analyses of depression. To date, only a few studies have included such variables (Heeren &

McNally, 2016; Hoorelbeke, Marchetti, De Schryver, & Koster, 2016). Whether rumination mediates the relation between affective bias and depressive symptoms is still not accounted for. For whom, and under which circumstances these interventions have reliable effects on depression symptoms is also under debate (Cristea, Kok, & Cuijpers, 2017; Grafton et al., 2017). The intervention of this clinical trial is a computerized training program, called affective bias modification (ABM), known to produce a generalized affective bias change (Browning, Holmes, Charles, Cowen, & Harmer, 2012). A main aim of this project is to investigate how the effects of this ABM intervention on depressive symptoms are mediated by transdiagnostic rumination and how characteristics of the symptom network moderate these effects.

2.1. Needs description. Depression affects more than 300 million people worldwide and is an increasing global health issue (Bender & Farvolden, 2008), however, treatment efficacy is still unsatisfying (Cuijpers, van Straten, Bohlmeijer, Hollon, & Andersson, 2010). Forty percent of patients do not, or only partially, respond to treatment and less than one-third are completely recovered after treatment (Andrews, Issakidis, Sanderson, Corry, & Lapsley, 2004). Furthermore, MDD with co-morbid anxiety predicts poor outcome with a higher percentage of treatment resistance than either disorder occurring alone (Coplan, Aaronson, Panthangi, & Kim, 2015), requiring new treatment options. While all available treatments of depression, psychologically as well as pharmacological, seem to be about equally effective, little is known about who benefits from which treatment (Cuijpers & Christensen, 2017). By combining an intervention based on transdiagnostic neuroscientific knowledge with *Ecological momentary assessment (EMA) of affective symptoms*, this study might contribute to close this knowledge gap.

Whether ABM directly changes rumination in transdiagnostic clinical patients and has not been systematically investigated previously. If successful, ABM could improve the outcome for patients where negative affective bias is central, for example as a supplement to treatment-as-usual. If effective, ABM expands the possibilities to choose non-pharmacological treatment options, which is important to many patients. The ABM intervention is highly scalable and is an economic way to alleviate symptoms, and can be done in the patients homes (Holmes et al., 2018). Combining EMA and personalized statistical approaches may provide a low-cost assessment method aiding clinicians in identifying the processes that are most likely maintaining symptoms. This assessment method can easily be modified to capture other relevant pathological dynamics (e.g., resilience, relational problems, other symptoms). Identifying these processes more precisely, will have the potential to make interventions more focused on the patient's problem, and lead to better treatment efficacy.

3. Hypotheses, aims and objectives.

Primary hypothesis: Subjects who are in the active ABM group will exhibit less tendency for stress related (state) rumination compared to those in the placebo group (2 weeks). Active vs placebo ABM will decrease depressive symptoms (6 months) and this effect will be mediated by the change in state rumination. Densely connected symptom network and high strength centrality of rumination at baseline will moderate the effect of ABM. See figure 3.

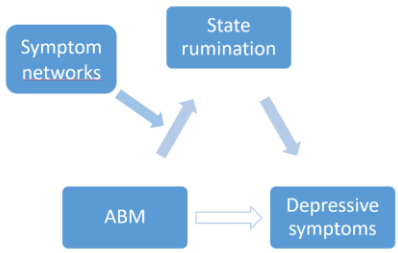

Figure 3. Model of the primary hypothesis

Secondary hypotheses: After the intervention, patients with changes in affective bias after ABM develop a less densely connected symptom network and have reduced strength centrality of rumination. Reduced network density and reduced strength centrality of rumination after ABM leads to reduction in depressive symptoms at 6 months.

4. Project methodology

*Design and participants***.** The Affective Bias Modification Task (ABM) will be applied in a randomized controlled, double blind clinical trial with 6 months follow-up. Personalized networks

are generated from prospective assessment of depression-related processes at baseline and follow-ups, allowing us to investigate for whom this procedure is effective. Patients (N = 150) will be recruited from an out-patient clinic at Diakonhjemmet Hospital, and randomized into one of three conditions: active, sham and assessment only. Patients aged 18-65 with depression (major depressive disorder) or bipolar disorder 2, with or without comorbid anxiety and/or alcohol use disorder will be included. Exclusion criteria are a history of mania, psychosis, or a neurological disorder.

4.1. Project arrangements, method selection and analyses.

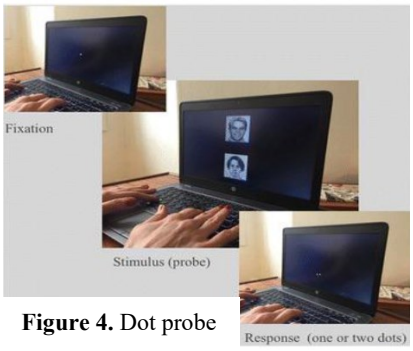

Figure 4. Dot probe

Negative affective bias. In the dot-probe task (MacLeod et al., 2002) paired stimuli (e.g. a negative and a positive face) are presented, followed by one or two probes (dots) appearing in the spatial location of one of the stimuli. See figure 4. Participants are then required to press one of two buttons as quickly as possible to indicate the number of dots in the probe. Thus, if the participant systematically orients towards a negative emotional stimulus (i.e. has a negative affective bias), they respond faster to probes presented at the spatial location of the negative stimulus compared to probes at the location of the positive stimulus. Stimuli presentation time is 50% 500 ms and 50 % 1000 ms (evenly distributed throughout the task). In total, the dot probe task will comprise 90 trials of paired images of faces of different valences.
The Facial Expression Recognition Task (FERT; (Harmer, O'Sullivan, et al., 2009) is another measure of negative affective bias and is included to make sure that biases measured with the dot probe task transfers to an independent measure. In this task, pictures of faces are gradually morphed between neutral, and positive and negative facial expressions. The detection threshold for correctly identifying the facial expression is the variable of interest.
Affective bias modification. The task is almost identical to the dot probe task. The differences are that the probe appears at the location of the most positive stimuli of each pair in 87 % of trials (encouraging a positive affective bias). In the control condition, there is no contingency between facial expressions shown and the probe location. Participants will do ABM in their homes (approx. 5 min.) twice a day for two weeks (28 sessions) using laptop computers provided by us. Our experience with previous ABM studies indicate good adherence by participants using this regime.
EMA of affective symptoms. The estimation of the each participant's symptom network is based on data from three separate two-weeks of EMA (baseline, follow-up and six months), conducted by means of the PsyMate^{TM}-app on their smartphones. The app pings four times per day (in the morning, middle of the day, afternoon, evening), at slightly irregular intervals, and instructs the participant to report on mood and symptoms guided by Positive and Negative Affective Schedule (PANAS; (Thompson, 2007)) and DSM-5 criteria of MDD, respectively, and the extent they have been engaged in brooding rumination. In total, the participant is pinged 56 times per two-week period and each self-report takes approximately 1 minute to complete.
Clinical and cognitive assessment. Diagnostic assessment will be made in accordance with the MINI International Neuropsychiatric Interview PLUS 5.0.0 (Sheehan et al., 2006). Depression symptoms will be assessed using Beck Depression Inventory – II (BDI-II; (Beck, Steer, & Brown, 1996)). Anxiety symptoms will be assessed using the Beck Anxiety Inventory (BAI; (Beck, Epstein, Brown, & Steer, 1988)). Trait rumination will be assessed by means of the Rumination Response Scale (RRS; (Treynor, Gonzalez, & Nolen-Hoeksema, 2003)). State rumination will be assessed by means of the Brief State Rumination Inventory (BSRI; Marchetti, Mor, Chiorri, & Koster, 2018). General attentional control will be assessed by the Attention Network Test (ANT; Fan, McCandliss, Fossella, Flombaum, & Posner, 2005).

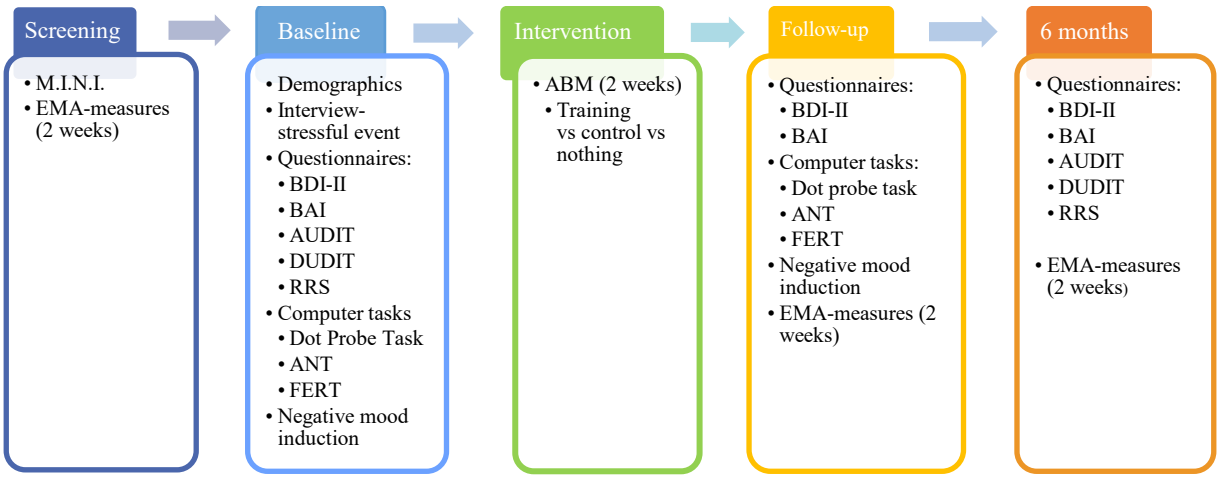

Figure 5. Design, procedures and schedule. ABM = Attention Bias Modification. AUDIT = Alcohol use disorder identification test. BAI = Beck Anxiety Inventory. BDI-II = Beck Depression Inventory - Second Edition. DUDIT = Drug use disorder identification test. EMA = Ecological Momentary Assessment. FERT= Facial expression recognition task. MINI = MINI International Neuropsychiatric Interview PLUS 5.0.0. RSS = Ruminative response scale.

Negative mood induction paradigm. Drawing on diathesis-stress models of affective disorder (Disner, Beevers, Haigh, & Beck, 2011), we will include a negative mood-induction procedure prior to assessment of state rumination and stress reactivity (Westermann, Stahl, & Hesse, 1996). A standardized mood induction script, personalized by stressful autobiographical events (Sinha & Tuit, 2012), will be recorded for each patient. Upon listening to the script, they are asked to imagine themselves being in the situation. Imagery vividness scale (Sinha & Tuit, 2012) is used to assess how clear they manage to imagine themselves in the situation. Afterwards, subjects will be left alone for five minutes to trigger state rumination. A shortened version of the Profile of Mood States (POMS; 37 items) will be administered before and after the mood induction as a manipulation check (Shacham, 1983). Our research group have previously shown that POMS reflects changes in mood states over short intervals in healthy controls (Walderhaug et al., 2007). Stress reactivity is operationalized as reduced HRV (measured via the Polar RS800 heart rate monitoring system) and rising cortisol levels (measured via Salivette® saliva sampling). A meta-analysis of cortisol response after stress induction has shown that peak cortisol is reached 38 minutes after stress induction onset (Goodman, Janson, & Wolf, 2017). Between post-induction and recovery, the participants will be encouraged to watch emotionally neutral videos (selected National Geographic films). See figure 6 for procedure and time schedule.

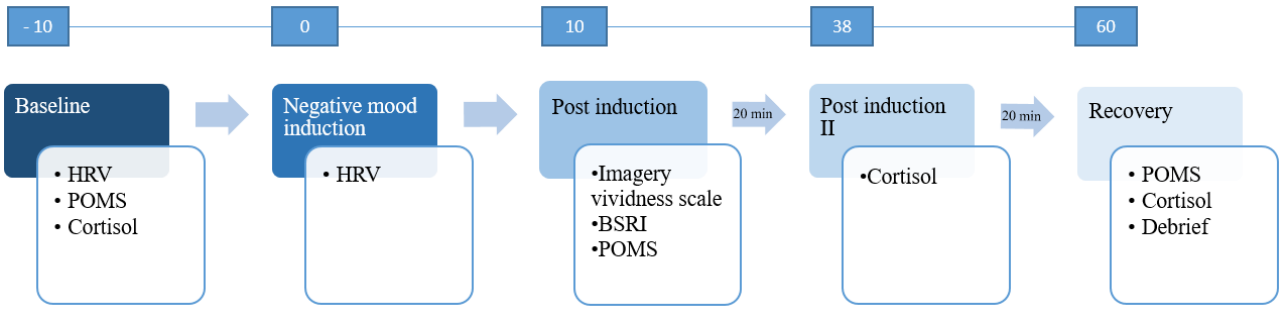

Figure 6. Negative mood induction procedure. BSRI = Brief state ruminative inventory. HRV = Heart rate variability. POMS = Profile of mood states.

Statistical power. Calculation of statistical strength regarding detecting an effect of ABM is based on an assumption that 20 % in the placebo group will report 3 points improvement on BDI-II at follow-up compared to 50 % in the active ABM group. The National Institute for Health and Care Excellence (NICE, 2009) , suggests a difference of ⩾3 BDI-II points is a clinically significant treatment effect for depression. By assuming 15 % drop-out at follow-up, 50 patients in each condition (total n= 100) will be required when 1 –β= .80 and α= .05. The literature provides no clear guidelines as to how many data points that is necessary to reliably estimate a patient's

symptom network, but simulation studies suggest adequate performance for estimating an eight-node network using 50 observations (Epskamp et al., 2018). Given multiple regression analysis with up to six predictors and a small effect size (<.10), β= .80 and α= .05, the estimated required sample size is 81. When examining the effect of ABM, we are only interested in effect sizes of clinical relevance (i.e. < 0.25). Given an ANOVA repeated measures analysis with effect size = 0.25, β= .80 and α= .05, the estimated required sample size to detect a difference in changes in the network metrics between the conditions is 34.

Mediation and moderation analysis. The mediation analysis, investigating whether the relation between ABM and symptoms change is mediated by rumination, will be performed according to the procedure established by Baron and Kenny (1986). The moderated mediation analysis, investigating whether ABM changes depressive symptoms as a function of symptom network, will be performed according to recommendations made by Muller, Judd, and Yzerbyt (2005).
Feasibility. Labs for conducting the research are available at the Department of psychology, University of Oslo. The biobank "Genes in cognition and Emotion" REK SørØst 2011/2593 will be used to store salvia samples. Twenty-five laptop computers for conducting the ABM-intervention and Polar watches for recording HRV are already acquired. Neurocognitive labs are available at the Department of Psychology. All questionnaires are translated into Norwegian by means of back translation procedures. The negative mood induction procedure will be piloted before commencement. The project is currently under evaluation by REK SørØst 2019/330. During the last decade, through our longstanding collaboration with Diakonhjemmet Hospital and other nearby clinics, we have managed to recruit hundreds of patients in different stages of their depressive illness to take part in clinical studies. The TSD (in Norwegian, Service for Sensitive Data) service will be used for storing and post-processing sensitive-data in compliance with the Norwegian "Personal Data Act" and "Health Reaserch Act". TSD is developed and maintained by USIT at the University of Oslo and supports research activities run at Norwegian public institutions.

4.2. Participants, organization and collaboration. The PI Professor Nils Inge Landrø (NIL) is an expert on the neuroscience of affective disorders. He has a part time position (20%) as research advisor at Diakonhjemmet Hospital. Postdoc Ragnhild Bø (RB) is currently involved in parts of this project through funding received from Extrastiftelsen. She has experience with research in cognition, emotion and alcohol use. Our research group, The Clinical Neuroscience Research Group (CNRG), have extensive experience with the ABM method and we have recently concluded a big randomized, double blind, placebo controlled, pre-registered study (ClinicalTrials.gov Identifier 02658682). In this study, formerly depressed persons (N = 321) were included with the main aim of reducing residual depression symptoms. Based on this study, five articles are accepted, one including network analysis, (Hilland, Landrø, Harmer, Browning, et al., 2018; Hilland, Landrø, Harmer, Maglanoc, & Jonassen, 2018; Jonassen et al., 2019; Kraft et al., 2019; Kraft, Jonassen, Ulset, Stiles, & Landrø, 2018).

The project builds on an established collaboration between CNRG at Department of Psychology, University of Oslo and Department of Psychiatry, Diakonhjemmet Hospital. Kåre Osnes, MD, PhD, specialist in psychiatry, Diakonhjemmet Hospital, is an expert in diagnostics and methodology, including statistics. Rune Jonassen, PhD and Associate Professor OsloMet, has experience with the ABM-procedure and biological underpinnings of depression. Professor Jutta Joormann, Department of Psychology, Yale University is an expert in state and trait rumination and attentional bias. Professor Alexander Heeren, Université Catholique de Louvain, is an expert on network analysis within the field of depression and anxiety. Professor Catherine J Harmer, University Department of Psychiatry, University of Oxford. She has also a Professor II position at Department of Psychology, University of Oslo and is affiliated to CNRG. She is an expert on experimental psychopathology, the ABM- procedure and implications of attentional bias change. NIL is the PI of the project. RB will be in charge of the day-to-day administration of the project, and coordinate team efforts. Collaborators will be involved if unexpected situations occur, if procedures needs to be adapted, when analyzing and interpreting data, and during writing of articles.

4.3. Budget. Please see the e-application for details.

4.4. Plan for activities, visibility and dissemination. This research program will be of considerable interest for a broad range of scientists and clinicians. The results will be published in in high-ranked peer-review journals in the fields of psychiatry, clinical and abnormal psychology and neuroscience. Main findings will be summarized and published in national journals, like The Journal of the Norwegian Medical Association and The Journal of the Norwegian Psychological Association. The results will also be relevant for people with affective disorders, family and friends, stakeholders and the general public. Thus, the main results and their implications will be disseminated to patients and the public through popular talks and newspapers, like Aftenposten and Dagbladet. We have an ongoing collaboration with Mental Helse, a nationwide volunteer organization promoting mental health. We will write blog posts about this ongoing project and main results, which will be published on their website. We will also publish summary of the main findings on forebygging.no, a national knowledgebase for promoting health, supported by the Norwegian Directorate of Health. This will be done in collaboration with the user representative. The researchers will be involved in more "popular" forms of dissemination, by actively participating at "Forskningsdagene" led by the Norwegian Research Council. We will also present the results of the project at events, such as Pecha Kucha or TedX.

4.5. Plan for implementation. There is a pressing need to improve treatment and thus clinical trials should focus not only on efficacy, but also on identification of the underlying mechanisms through which treatment operate and within a transdiagnostic frame. Biased attention towards negative stimuli is such a mechanism, cutting across diagnostic boundaries and is also related to dysfunctional rumination and stress reactivity. These mechanisms can be targeted separately applying a simple behavioral procedure, The Attention Bias Modification Task; ABM. Should this project be successful, ABM can easily by implemented into the clinics. Most people have their own computer, and may perform the ABM-task at home if instructed to do so by their therapists. Opportunities for online downloading of ABM software are then required. The app used for extracting the patient symptom networks are readily available, and may guide treatment recommendation following the results of the current project. Today, treatments such as cognitive behavioral therapy and antidepressant medication might change affective biases (Bowler et al., 2012; Harmer, Goodwin, & Cowen, 2009); however, by implementing ABM we could more readily target these biases. By combining ABM with today's treatment options, we could potentially increase treatment efficacy and shorten treatment duration. Furthermore, the symptom network approach allows treatment to be personalized and adapted to each patient's specific symptom profile. This is in contrast to the current "one size fits all"-approach. Hence, this research has the potential for improving treatment outcomes for persons with depression and comorbid disorder, and thus release resources in the health services. Therefore, we will work actively to ensure that computerized cognitive interventions, such as ABM, combined with the symptom network approach, will be considered supplement to treatment-as-usual in national clinical guidelines for these disorders. In collaboration with DigPsyk, an interest organization promoting the use of technology in treatment of psychological problems and that is part of the Norwegian Psychological Association; we will disseminate the methodologies employed in this project. The use of technology in treatment for psychological problems is gradually paving its way into the clinics; however, there is still some way to go before technology is a go-to method for treating psychological problems. Strong studies, like this, which is thoroughly disseminated to both users and clinicians, in combination with a low-cost, easy-to-use platform implemented at patient homes, makes it readily feasible as a treatment.

5. User involvement

In clinics, drug free treatment options are sought after. Our project is rooted in the user organization Mental Helse. One person from this organization will help us plan the project and adapt it according to patient needs, ensuring that patients are given adequate information and that the working load on

behalf of participants is adequate. This will help us recruit patients and prevent drop-out, which is among the major risks associated with this project. This person will also help disseminate the results of the current project, in particular in fora outside of academia. By interviewing a focus group of research participants, we will gather their opinion on the ABM-procedure and the EMA. By adapting the procedures according to their experiences and suggestions, we will ensure that they are acceptable to patients. We will also interview therapists as to what they need in order to recommend this type of treatment to their patients. Should the project be successful, this will allow us more readily to implement these procedures in clinics, who then could offer personalized drug-free treatment options as supplement to treatment as usual.

6. Ethical consideration.

The project is currently under review by the Regional Committee for medical and health research ethics (REK SørØst 2019/33). In particular, the potential negative consequences following the negative mood induction procedure will need to be justified, even when this procedure is commonly used. We will provide appropriate help should participants experience subsequent problems associated with it. Except from this, there is no reason to believe that the project will lead to undesirable effects, except from the time spent on behalf of the individual participants. Salvia samples will be stored in the biobank "Genes in cognition and Emotion" (REK SørØst 2011/2593) and used solely in relation to this project.

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