Study protocol: an investigation of general predictors for cognitive behavioral therapy outcome for anxiety disorders in a naturalistic setting

<table>
<thead>
<tr>
<th>Journal:</th>
<th>BMJ Open</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manuscript ID</td>
<td>bmjopen-2015-010898</td>
</tr>
<tr>
<td>Article Type:</td>
<td>Protocol</td>
</tr>
<tr>
<td>Date Submitted by the Author:</td>
<td>17-Dec-2015</td>
</tr>
<tr>
<td>Complete List of Authors:</td>
<td>Nielsen, Sara; University of Copenhagen, Department of Psychology Vangkilde, Signe; University of Copenhagen, Psychology Wolitzky-Taylor, Kate; University of California, Department of Psychiatry and Biobehavioral Sciences Semel Institute Daniel, Sarah; University of Copenhagen, Psychology Hageman, Ida; Rigshospitalet, Psychiatric Centre</td>
</tr>
<tr>
<td>Primary Subject Heading:</td>
<td>Mental health</td>
</tr>
<tr>
<td>Secondary Subject Heading:</td>
<td>Evidence based practice</td>
</tr>
<tr>
<td>Keywords:</td>
<td>MENTAL HEALTH, Anxiety disorders &lt; PSYCHIATRY, Adult psychiatry &lt; PSYCHIATRY</td>
</tr>
</tbody>
</table>
Title:

Study protocol: an investigation of general predictors for cognitive behavioral therapy outcome for anxiety disorders in a naturalistic setting

Corresponding author:

Sara Kerstine Kaya Nielsen, University of Copenhagen, Department of Psychology, Øster Farimagsgade 2A, 1353 Copenhagen K, Denmark, email: Sara.nielsen@psy.ku.dk, Telephone: 0045 35 32 48 96

Coauthors:

Signe Vangkilde, University of Copenhagen, Department of Psychology, Copenhagen, Denmark.

Kate B. Wolitzky-Taylor, University of California, Department of Psychiatry and Biobehavioral Sciences Semel Institute, Los Angeles, USA.

Sarah Ingrid Franksdatter Daniel, University of Copenhagen, Department of Psychology, Copenhagen, Denmark.

Ida Hageman, Copenhagen University Hospital, Psychiatric Centre Copenhagen, Denmark.

Keywords: Mental health, anxiety, cognitive behavioral therapy, predictors, treatment efficacy

Word count: 2101
Study protocol: an investigation of general predictors for cognitive behavioral therapy outcome for anxiety disorders in a naturalistic setting

Sara Kerstine Kaya Nielsen, Signe Vangkilde, Kate B. Wolitzky-Taylor, Sarah Ingrid Franksdatter Daniel, & Ida Hageman

1 Department of Psychology, University of Copenhagen, Denmark
2 Department of Psychiatry and Biobehavioral Sciences Semel Institute, University of California, USA
3 Psychiatric Centre Copenhagen, Copenhagen University Hospital, Denmark

Abstract

Introduction: Cognitive behavioral therapy (CBT) is effective for treating anxiety disorders and is offered in most mental health services around the world. However, a relatively large number of patients with anxiety disorders do not benefit from CBT, experience relapses, or drop out. Reliable predictors of treatment effects are lacking. The aim of this study is to investigate the predictive value of emotion regulation and attentional control for CBT outcome in a naturalistic setting.

Methods and analysis: In this prospective and naturalistic study, 110 patients with anxiety disorders referred for manual-based group CBT at two psychiatric outpatient clinics will be recruited. Patients will be assessed at baseline, post-treatment, and at a 6-month follow-up. Emotion regulation will be measured with Difficulties in Emotion Regulation Questionnaire, severity of anxiety will assessed with Beck Anxiety Inventory, and attentional control will be measured with the self-report questionnaire Attention Control Scale and with an experimental computer-based attentional control task based upon Theory of Visual Attention. To examine the main objective of this study; a mixed effects, repeated measures analysis of covariance (ANCOVA) model will be used.

Ethics and dissemination: The Danish National Ethical Board is notified about the study and the study is approved by Department of Psychology Ethical Board, University of Copenhagen, and by the Danish Data Protection Agency. Study findings will be disseminated through peer-reviewed journal publications and conference presentations.
Introduction

Anxiety disorders are a pervasive problem, with an estimated 12-month prevalence of 16.6% (1), and they are associated with significant impairment (2) and high social costs (3). Cognitive behavioral therapy (CBT) has shown to be effective and for treating of anxiety disorders. (see, (4) for meta-analytic review) CBT is furthermore cost-effectiveness. (5) This has made CBT the first choice of treatment for anxiety disorders in many mental health settings around the world. Despite this impressive evidence-base, a relatively large group of individuals do not benefit from CBT, relapse, or drop out of treatment. (6) Thus, there is a clear and pressing need to improve the efficacy and effectiveness of CBT for anxiety disorders. One way in which to improve is to identify predictors of CBT outcome. In naturalistic clinical settings, identification of prognostic factors can help allocate resources to those presumed to benefit most from CBT, while also identifying those who may need additional CBT, adjunctive therapy, or entirely different treatment to maximize outcomes.

Current knowledge about who is most likely to benefit from CBT is sparse and stems primarily from well-controlled laboratory settings. These results may not generalize to patient outcomes in mental health settings, in which patients with more severe and comorbid disorders are often seen. (7), (8), (9) Thus, naturalistic studies have the potential to significantly increase knowledge, inform clinical strategies, and thus improve the treatment offered in mental health settings. Furthermore, existing studies have mostly investigated socio-demographic factors as predictors of drop-out and non-response. However, these variables have shown to be either non-significant or inconsistent predictors of outcome. (10) Results concerning comorbidity as a predictor are also mixed. (11, 12) In sum, knowledge on who is most likely to benefit from CBT is sparse, and to date no reliable predictors have been identified. (13, 14)

While prior work has primarily emphasized atheoretical predictors, it may prove more fruitful to focus on predictor variables stemming from psychological theories. Identifying such predictors can provide direct prognostic information for clinicians. Additionally, these predictors could also inform the development of adjunctive components of treatment that may optimize the treatment for those with poorer CBT outcome. Some exciting studies suggest that such a line of inquiry could yield relevant results. (15, 16)
Maintaining factors is one aspect highlighted by several therapeutic approaches/theories as crucial for the treatment of anxiety disorders, and accordingly these factors are often the target of cognitive and behavioral treatments. Emotion regulation and attentional control are examples of key maintaining factors in anxiety disorders. (17–22) CBT, which aims to teach patients cognitive reappraisal of maladaptive cognitions and encourages approach (rather than avoidance) behavior via cognitive restructuring and exposure, (23) may be more suitable for patients with certain characteristics. Specifically, recent research and theory suggest that it is crucial for effective treatment of anxiety disorders that clients learn to tolerate fear while being exposed to anxiety-provoking stimuli, rather than merely habituating to the stimuli. (24) Learning to tolerate fear may require emotion regulation skills and the ability to control attention and this has been supported by recent studies. (24) However, so far only certain areas of emotion regulation have been investigated and to date never in a naturalistic setting. Attentional control has never been examined as a predictor of CBT outcomes. Accordingly, this study is designed to investigate the predictive value of attentional control and of three facets of emotion regulation skills.

**Attentional control**

There is strong evidence that individuals with anxiety disorders have biased attention towards threatening stimuli, (17) but there is no consensus as to why these biases occur. Recent research suggests that it is not the threat bias per se that is problematic. Rather, individual differences in the ability to voluntarily control attention may affect the impact of threatening information hence increasing or decreasing the anxiety symptoms. (19,20) A potential consequence may be that individuals with low ability to voluntarily control their attention have difficulties participating in exposure and/or do not progress in the exposure hierarchy, because the level of anxiety gets too high. This may subsequently lead to failure to learn that fear is not dangerous or even drop-out of CBT. Furthermore, a pronounced bias towards irrelevant negative information may take up so many resources that processing of important, relevant information is hampered, making it difficult to engage in goal-oriented behavior while experiencing anxiety.
Emotion regulation as predictor

Novel theoretical frameworks emphasize that difficulties in emotion regulation are associated with the development and maintenance of anxiety disorders. (e.g., (25, 26, 18)) Additionally, emotion regulation skills may be required to engage in and benefit from CBT. (22, 24) Furthermore, in an attempt to increase effectiveness, several newer treatments have included emotion regulation training in their treatments protocols. (27, 28, 22)

The present study aims to examine attentional control and three facets of emotion regulation: 1) awareness and understanding of emotions, 2) acceptance of emotions, and 3) the ability to engage in goal-directed behavior, and refrain from impulsive behavior, when experiencing negative emotions as general predictors of outcome in CBT for anxiety disorders in a naturalistic, community-based mental health setting. Our secondary aim is to examine atheoretical variables (i.e., socio-demographic data and clinical characteristics, such as comorbidity) as predictors of CBT outcome, as these have yet to be examined as predictors in real-world clinical settings in a mixed anxious sample.

We expect that low ability to control attention will be associated with poorer treatment outcome. Similarly, it is expected that high scores on emotion dysregulation will be related to poorer treatment outcome. Given the exploratory nature of this study we will also be interested in testing non-linear relationships. (see (15))

Method

In order to maximize external validity we are conducting the study within two real-world treatment clinics and employing minimal exclusion criteria recruiting a sample with mixed principal anxiety disorders.

Participants

Patients (N=110) with anxiety disorders (social anxiety, generalized anxiety disorder, panic disorder and agoraphobia) referred for treatment, from general practitioners, hospital units, or private psychiatrists to two outpatients clinics of the Mental Health System in the Capital Region of
Copenhagen will be included. All patients referred to the psychiatric clinics will have a full psychiatric examination by a psychiatrist, who makes the preliminary psychiatric diagnoses in accordance to ICD-10.(29) Eligible patients are then interviewed by either a psychiatrist or a trained psychologist using the anxiety part of the MINI-International Neuropsychiatric Interview(30) to assess whether the patient fulfills the criteria for an anxiety disorder according to the Diagnostic and statistical manual of mental disorders (5th ed.).(31) The MINI is a brief, structured diagnostic interview with excellent validity and interrater reliability.(30)

Patients will be eligible for the study if they a) meet the diagnostic criteria for an anxiety disorder (social anxiety, generalized anxiety, panic disorder and agoraphobia) as primary diagnosis whether first episode or recurrent, b) are between 18 to 60 years of age, c) provide written informed consent, and d) speak and understand Danish. Exclusion criteria include: a) cognitive disabilities (assessed with subscales from Wechsler Adult Intelligence Scale Fourth-Edition, < 70), b) alcohol or substance abuse (assessed during the preliminary consultations), or c) receiving any other psychotherapy during the study. Patients receiving medical treatment (e.g., antidepressants, Benzodiazepines) will also be included in the study and the treatment will be monitored closely.

**Intervention**

The participants will receive 12-16 sessions of manualized group-based CBT with a maximum of 8 participants in each group. The therapists are trained psychiatrists, psychologists, or nurses under supervision. The treatment manuals are developed by mental health professionals in the Capital Region of Denmark. The treatment program includes traditional CBT components (e.g., psychoeducation, identification of thoughts and feelings, exposure, cognitive restructuring, and relapse prevention).

**Measures**

The participants will be assessed with the following measures at pre- and post-treatment and at 6-months follow-up.
Primary outcome measure

Beck Anxiety Inventory (BAI). (32) Because this study includes patients with mixed anxiety disorders, an outcome measure that measures general anxiety symptoms has been chosen. BAI is a widely used questionnaire and has 21 items measuring the intensity of general anxiety symptoms. BAI has shown high internal consistency (α = .92) and high test-retest reliability, r(81) = .75. (32)

Secondary outcome measure

Symptom checklist 90-revised (SCL-90-R). (33) To measure general symptoms the SCL-90-R will be used. The SCL-90 is a self-administered questionnaire measuring symptoms on one global scale and nine subscales: somatization, obsessive-compulsive symptoms, interpersonal sensitivity, depression, anxiety, hostility, phobic-anxiety, paranoid ideation, and psychoticism. The scale has good test-retest reliability, internal consistency, and construct validity. (33)

Potential predictors

Difficulties in Emotion Regulation Questionnaire (DERS). (34) DERS is a 36-item scale designed to assess to which extent difficult emotions are impacting daily life. The DERS provides an overall score of difficulties in emotion regulation and taps six specific factors related to emotion dysregulation: 1) nonacceptance: nonacceptance of emotional responses, 2) goals: difficulty engaging in goal-oriented behaviors, 3) impulse: difficulty controlling impulses, 4) awareness: lack of emotional awareness, 5) strategies: lack of access to emotion regulation strategies, and 6) clarity: lack of emotional clarity. The scale has high internal consistency (α = .93). (34)

Attention Control Scale (ACS). (19,35) The ACS is a 20-item self-report scale designed to measure two major components of attention: focusing and shifting of attention. Specifically, the ACS measures the experienced ability to focus and shift attention voluntarily. The ACS is widely used to assess executive functions and has high internal consistency (α = .88). (35)
Theory of Visual Attention (Emotional CombiTVA paradigm) (TVA)(36)

This study will use the Theory of Visual Attention (TVA)(37) as a framework for investigating attentional functions and attentional bias in the participants. TVA is a formal computational theory that describes attention as a set of processes, which allow us to select the information that is currently relevant for behavior. The specific paradigm used in this study, the CombiTVA,(38) taps several attentional core functions such as how much material can be stored in visual short-term memory (VSTM) and how fast visual information can be processed. Furthermore, it is possible to measure the threshold of conscious perception and the selectivity of attention, as well as to characterize how participants distribute their attention over space. TVA-based assessment of attention has primarily been conducted using simple, non-emotional stimuli (e.g., letters, digits, words, or simple figures), however, in this project, we will introduce the use of emotional stimuli in the CombiTVA paradigm (for a preliminary TVA-based study employing stylized emotional faces see(36)). This will enable us to estimate whether e.g. negative emotional stimuli are attended preferentially or avoided, processed faster or slower, and if they affect the capacity of visual short-term memory differently compared to neutral stimuli.

Sample Size

Sample size calculations are based on a moderate effect size at the conventional $\alpha$ level of .05. A total of 110 patients are needed to power the study sufficiently and detect an increase from 50% to 55% in explained variance in a two-parameter regression model at a two-tailed significance level of 5%.

Data analysis

To examine the effect of treatment on the outcome measure (i.e., Beck Anxiety Inventory (BAI) and Symptom Check List 90-R (SCL-90-R)), we will use a repeated measures analysis of variance (ANOVA) model. To examine the main objective of this study; how attentional control and emotion regulation affect the result at post-treatment, we will use a mixed effects, repeated measures analysis of covariance (ANCOVA) model. Like recent studies,(15) we will treat the repeated measures of BAI as the dependent variable, and time as independent variable, and test for potential prediction by adding
the potential predictor variables as measured at baseline as covariates. To explore non-linear relationships we will add the quadratic effects of attentional control and emotion regulation at baseline. The clustering of patients will be accounted for by inclusion of a therapist-specific random intercept. In order to investigate if there is a difference between treatment completers and drop-outs, we will use a multivariate analysis of variance with baseline measures of BAI and the potential predictors. To account for missing data we will use multiple imputation.

**Ethics and dissemination**

The study is approved by the Ethical Board, Department of Psychology, University of Copenhagen and by the Danish Data Protection Agency (OK308627) and personal data about the respondents are thus protected according to cf. section 50(1)(i) of the Danish Act on Processing of Personal Data. Moreover, the Danish Committee System on Health Research Ethics was informed of the project. The committee found that the project did not need separate ethical approval, since it does not include any biomedical intervention. Study findings will be disseminated through peer-reviewed publications and conference presentations.

**Author contributions**

SKKN and SV have primarily designed the study. IH, SD and KWT have contributed with analysis/research design input. SKKN wrote the first draft of this paper. All authors read, commented and approved the final paper.

**Funding**

The work is supported by Kristian Holt Hansen Foundation and Aase & Ejnar Danielsen Foundation.

**Competing interests**

None
References


An investigation of general predictors for cognitive behavioral therapy outcome for anxiety disorders in a routine clinical setting

<table>
<thead>
<tr>
<th>Journal:</th>
<th>BMJ Open</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manuscript ID</td>
<td>bmjopen-2015-010898.R1</td>
</tr>
<tr>
<td>Article Type:</td>
<td>Protocol</td>
</tr>
<tr>
<td>Date Submitted by the Author:</td>
<td>16-Feb-2016</td>
</tr>
<tr>
<td>Complete List of Authors:</td>
<td>Nielsen, Sara; University of Copenhagen, Department of Psychology Vangkilde, Signe; University of Copenhagen, Psychology Wolitzky-Taylor, Kate; University of California, Department of Psychiatry and Biobehavioral Sciences Semel Institute Daniel, Sarah; University of Copenhagen, Psychology Hageman, Ida; Rigshospitalet, Psychiatric Centre</td>
</tr>
<tr>
<td>Primary Subject Heading:</td>
<td>Mental health</td>
</tr>
<tr>
<td>Secondary Subject Heading:</td>
<td>Evidence based practice</td>
</tr>
<tr>
<td>Keywords:</td>
<td>MENTAL HEALTH, Anxiety disorders &lt; PSYCHIATRY, Adult psychiatry &lt; PSYCHIATRY</td>
</tr>
</tbody>
</table>
An investigation of general predictors for cognitive behavioral therapy outcome for anxiety disorders in a routine clinical setting

Sara Kerstine Kaya Nielsen1*, Signe Vangkilde1, Kate B. Wolitzky-Taylor2, Sarah Ingrid Franksdatter Daniel1, & Ida Hageman3

1 Department of Psychology, University of Copenhagen, Denmark
2 Department of Psychiatry and Biobehavioral Sciences Semel Institute, University of California, USA
3 Psychiatric Centre Copenhagen, Copenhagen University Hospital, Denmark

*corresponding author

Abstract

Introduction: Cognitive behavioral therapy (CBT) is effective for treating anxiety disorders and is offered in most mental health services around the world. However, a relatively large number of patients with anxiety disorders do not benefit from CBT, experience relapses, or drop out. Reliable predictors of treatment effects are lacking. The aim of this study is to investigate the predictive value of emotion regulation and attentional control for CBT outcome in a routine setting.

Methods and analysis: In this prospective and practice-based study, 112 patients with anxiety disorders referred for manual-based group CBT at two psychiatric outpatient clinics will be recruited. Emotion regulation, severity of anxiety, and attentional control will be assessed with self-report measures and with an experimental computer-based attentional control task at baseline, post-treatment, and at a 6-month follow-up. Emotion regulation will be measured with Difficulties in Emotion Regulation Questionnaire, severity of anxiety will assessed with Beck Anxiety Inventory, and attentional control will be measured with the self-report questionnaire Attention Control Scale and with an experimental computer-based attentional control task based upon Theory of Visual Attention. Data will be analyzed using multilevel mixed effects modeling.

Ethics and dissemination: The study is approved by the Danish National Ethical Board, the Department of Psychology Ethical Board, University of Copenhagen, and by the Danish Data Protection Agency. Study findings will be disseminated through peer-reviewed journal publications
and conference presentations. Danish Committee System on Health Research Ethics has notified about the project.

**Strengths and limitations of this study:**

- Practice-based study
- Theory-based predictors
- Combining experimental and self-report measures
- Large sample size
- Lack of untreated control group
- Length of follow-up

**Introduction**

Anxiety disorders are a pervasive problem, with an estimated 12-month prevalence of 16.6 % (1), and they are associated with significant impairment (2) and high social costs. (3) Cognitive behavioral therapy (CBT) has shown to be effective and for treating of anxiety disorders. (see, (4) for meta-analytic review) CBT is furthermore cost-effectiveness. (5) This has made CBT the first choice of treatment for anxiety disorders in many mental health settings around the world. Despite this impressive evidence-base, a relatively large group of individuals do not benefit from CBT, relapse, or drop out of treatment. (6) Thus, there is a clear and pressing need to improve the efficacy and effectiveness of CBT for anxiety disorders. One way in which to improve is to identify predictors of CBT outcome. In routine clinical settings, identification of prognostic factors can help allocate resources to those presumed to benefit most from CBT, while also identifying those who may need additional CBT, adjunctive therapy, or entirely different treatment to maximize outcomes.

Current knowledge about who is most likely to benefit from CBT is sparse and stems primarily from well-controlled laboratory settings. These results may not generalize to patient outcomes in mental health settings, in which patients with more severe and comorbid disorders are often seen. (7,8,9,10) Thus, practice-based studies (i.e. studies conducted in routine clinical settings) have the potential to significantly increase knowledge, inform clinical strategies, and thus improve the treatment offered in mental health settings. (10) Furthermore, existing studies have mostly
investigated socio-demographic factors as predictors of drop-out and non-response. However, these variables have shown to be either non-significant or inconsistent predictors of outcome.(11) Results concerning comorbidity as a predictor are also mixed.(12,13) In sum, knowledge on who is most likely to benefit from CBT is sparse, and to date no reliable predictors have been identified.(14,15)

While prior work has primarily emphasized atheoretical predictors, it may prove more fruitful to focus on predictor variables stemming from psychological theories. Identifying such predictors can provide direct prognostic information for clinicians. Additionally, these predictors could also inform the development of adjunctive components of treatment that may optimize the treatment for those with poorer CBT outcome. Some exciting studies suggest that such a line of inquiry could yield relevant results.(16,17)

Maintaining factors is one aspect highlighted by several therapeutic approaches/theories as crucial for the treatment of anxiety disorders, and accordingly these factors are often the target of cognitive and behavioral treatments. Emotion regulation and attentional control are examples of key maintaining factors in anxiety disorders.(18–23)

CBT, which aims to teach patients cognitive reappraisal of maladaptive cognitions and encourages approach (rather than avoidance) behavior via cognitive restructuring and exposure,(24) may be more suitable for patients with certain characteristics. Specifically, recent research and theory suggest that it is crucial for effective treatment of anxiety disorders that clients learn to tolerate fear while being exposed to anxiety-provoking stimuli, rather than merely habituating to the stimuli.(25) Learning to tolerate fear may require emotion regulation skills and the ability to control attention and this has been supported by recent studies.(25) However, so far only certain areas of emotion regulation have been investigated and to date never in a routine clinical setting. Attentional control has never been examined as a predictor of CBT outcomes. Accordingly, this study is designed to investigate the predictive value of attentional control and of three facets of emotion regulation skills.

**Attentional control**

There is strong evidence that individuals with anxiety disorders have biased attention towards threatening stimuli,(18) but there is no consensus as to why these biases occur. Recent research
suggests that it is not the threat bias per se that is problematic. Rather, individual differences in the ability to voluntarily control attention may affect the impact of threatening information hence increasing or decreasing the anxiety symptoms. (20, 21) A potential consequence may be that individuals with low ability to voluntarily control their attention have difficulties participating in exposure and/or do not progress in the exposure hierarchy, because the level of anxiety gets too high. This may subsequently lead to failure to learn that fear is not dangerous or even drop-out of CBT. Furthermore, a pronounced bias towards irrelevant negative information may take up so many resources that processing of important, relevant information is hampered, making it difficult to engage in goal-oriented behavior while experiencing anxiety.

**Emotion regulation as predictor**

Novel theoretical frameworks emphasize that difficulties in emotion regulation are associated with the development and maintenance of anxiety disorders. (e.g. (19, 26, 27)) Additionally, emotion regulation skills may be required to engage in and benefit from CBT. (23, 25) Furthermore, in an attempt to increase effectiveness, several newer treatments have included emotion regulation training in their treatments protocols. (23, 28, 29)

The present study aims to examine attentional control and three facets of emotion regulation: 1) **awareness and understanding of emotions**, 2) **acceptance of emotions**, and 3) **the ability to engage in goal-directed behavior, and refrain from impulsive behavior, when experiencing negative emotions** as general predictors of outcome in CBT for anxiety disorders in a community-based mental health setting. Our secondary aim is to examine atheoretical variables (i.e., socio-demographic data and clinical characteristics, such as comorbidity) as predictors of CBT outcome, as these have yet to be examined as predictors in real-world clinical settings in a mixed anxious sample.

We expect that low ability to control attention will be associated with poorer treatment outcome. Similarly, it is expected that high scores on emotion dysregulation will be related to poorer treatment outcome. Given the exploratory nature of this study we will also be interested in testing non-linear relationships. (see (16))
Method

In order to maximize external validity we are conducting the study within two real-world treatment clinics and employing minimal exclusion criteria recruiting a sample with mixed principal anxiety disorders.

Participants

Patients (N=112) with anxiety disorders (social anxiety, generalized anxiety disorder, panic disorder and agoraphobia) referred for treatment, from general practitioners, hospital units, or private psychiatrists to two outpatients clinics of the Mental Health System in the Capital Region of Copenhagen will be included. All patients referred to the psychiatric clinics will have a full psychiatric examination by a psychiatrist, who makes the preliminary psychiatric diagnoses in accordance to ICD-10.(30) Eligible patients are then interviewed by either a psychiatrist or a trained psychologist using the anxiety part of the MINI-International Neuropsychiatric Interview(31) to assess whether the patient fulfills the criteria for an anxiety disorder according to the Diagnostic and statistical manual of mental disorders (5th ed.).(32) The MINI is a is a brief, structured diagnostic interview with excellent validity and interrater reliability.(31)

Patients will be eligible for the study if they a) meet the diagnostic criteria for an anxiety disorder (social anxiety, generalized anxiety, panic disorder and agoraphobia) as primary diagnosis whether first episode or recurrent, b) are between 18 to 60 years of age, c) provide written informed consent, and d) speak and understand Danish. Exclusion criteria include: a) cognitive disabilities (assessed with subscales from Wechsler Adult Intelligence Scale Fourth-Edition, < 70), b) alcohol or substance abuse (assessed during the preliminary consultations), or c) receiving any other psychotherapy during the study. Patients receiving medical treatment (e.g., antidepressants, Benzodiazepines) will also be included in the study and the treatment will be monitored closely.

Intervention
The participants will receive 12-16 sessions of manualized group-based CBT with a maximum of 8 participants in each group. The therapists are trained psychiatrists, psychologists, or nurses under supervision. The treatment manuals are developed by mental health professionals in the Capital Region of Denmark. The treatment program includes traditional CBT components (e.g., psychoeducation, identification of thoughts and feelings, exposure, cognitive restructuring, and relapse prevention).

Measures

The participants will be assessed with the following measures at pre- and post-treatment and at 6-months follow-up.

Primary outcome measure

Beck Anxiety Inventory (BAI). (33) Because this study includes patients with mixed anxiety disorders, an outcome measure that measures general anxiety symptoms has been chosen. BAI is a widely used questionnaire and has 21 items measuring the intensity of general anxiety symptoms. BAI has shown high internal consistency ($\alpha = .92$) and high test-retest reliability, $r(81) = .75$. (33)

Secondary outcome measure

Symptom checklist 90-revised (SCL-90-R). (34) To measure general symptoms the SCL-90-R will be used. The SCL-90 is a self-administered questionnaire measuring symptoms on one global scale and nine subscales: somatization, obsessive-compulsive symptoms, interpersonal sensitivity, depression, anxiety, hostility, phobic-anxiety, paranoid ideation, and psychoticism. The scale has good test-retest reliability, internal consistency, and construct validity. (34)

Potential predictors

Difficulties in Emotion Regulation Questionnaire (DERS). (35) DERS is a 36-item scale designed to assess to which extent difficult emotions are impacting daily life. The DERS provides an overall score
of difficulties in emotion regulation and taps six specific factors related to emotion dysregulation: 1) 
nonacceptance: nonacceptance of emotional responses, 2) goals: difficulty engaging in goal-oriented 
behaviors, 3) impulse: difficulty controlling impulses, 4) awareness: lack of emotional awareness, 5) 
strategies: lack of access to emotion regulation strategies, and 6) clarity: lack of emotional clarity. The 
scale has high internal consistency (α = .93).(35)

Attention Control Scale (ACS).(20,36) The ACS is a 20-item self-report scale designed to measure two 
major components of attention: focusing and shifting of attention. Specifically, the ACS measures the 
experienced ability to focus and shift attention voluntarily. The ACS is widely used to assess executive 
functions and has high internal consistency (α = .88).(36)

Theory of Visual Attention (Emotional CombiTVA paradigm) (TVA).(37)

This study will use the Theory of Visual Attention (TVA)(38) as a framework for investigating 
attentional functions and attentional bias in the participants. TVA is a formal computational theory 
that describes attention as a set of processes, which allow us to select the information that is 
currently relevant for behavior. The specific paradigm used in this study, the CombiTVA,(39) taps 
several attentional core functions such as how much material can be stored in visual short-term 
memory (VSTM) and how fast visual information can be processed. Furthermore, it is possible to 
measure the threshold of conscious perception and the selectivity of attention, as well as to 
characterize how participants distribute their attention over space. TVA-based assessment of 
attention has primarily been conducted using simple, non-emotional stimuli (e.g., letters, digits, 
words, or simple figures), however, in this project, we will introduce the use of emotional stimuli in 
the CombiTVA paradigm (for a preliminary TVA-based study employing stylized emotional faces 
see(37)). This will enable us to estimate whether e.g. negative emotional stimuli are attended preferentially or avoided, processed faster or slower, and if they affect the capacity of visual short-
term memory differently compared to neutral stimuli.

Sample Size
To calculate the sample size and power, we used G*Power 3.1. First, sample size was calculated concerning the primary outcome, BAI. Previous studies have indicated reductions in BAI score after CBT treatment corresponding to effect sizes (Cohen’s d) between 0.44-0.87. (40,41) Choosing a conservative estimate of 0.44, we need a sample of 57 patients to power the study sufficiently (90%) at an alpha-level of 5%. Second, we calculated the required sample size for one of the predictors, DERS. A total of 84 patients is needed to obtain a power of 90 % and detect a 5% increase in the explained variance in Post BAI score when Pre DERS score is included as additional predictor in a regression model with Pre BAI score and Pre DERS score as predictors at a two-tailed significance level of 5% and assuming a BAI test-retest effect of $r = 0.75$. (33) Previous predictor studies in the field of anxiety disorders(13,16,42) have indicated a drop-out rate of approx. 25 % from baseline to follow-up. Hence, we aim to recruit 112 participants to make up for the expected loss of participants.

**Data analysis**

Our overall approach to data analysis will be linear mixed model regression analyses, in which the clustering of patients will be accounted for by inclusion of therapist-specific and group-specific random intercepts if necessary as judged based on levels of between-group variance in the outcome and model fit. Patients will be considered treatment completers if they have attended at least 9 therapy sessions. In order to investigate if there is a difference between treatment completers and drop-outs, baseline measures of BAI, SCL 90 R, DERS, ACS, and CombiTVA variables will be used as predictors of treatment completion vs. drop-out in a logistic regression analysis.

The primary outcome measure (BAI) is measured at three time points: Baseline, post-treatment, and six-month follow-up, rather than as more continuous measures during treatment. This makes the fitting of growth curves inappropriate, and similar to recent studies(16) we will therefore employ a mixed effects, ANCOVA-like design. Baseline BAI will be included as a between-subjects covariate, and the two post-treatment assessments will be treated as two levels of the repeated-measures independent variable (TIME: post-treatment vs. follow-up). The repeated measures covariance
structure will be chosen based on optimal model fit. Missingness is only expected on the outcome variable, and this analytical strategy will allow us to include all patients with at least one post-treatment measurement of the outcome. To examine the main objective of this study: how attentional control and emotion regulation affect anxiety levels post-treatment, we will include the potential predictor variables as measured at baseline as covariates, both as main effects and in interaction with the TIME variable. A significant main effect of the predictor variable will indicate that the variable predicts post-treatment BAI while taking baseline BAI levels into account. A significant interaction between the predictor variable and TIME will indicate that this effect differs for the post-treatment and follow-up measurements. To explore non-linear relationships we will also add the quadratic effects of predictor variables in a second analysis step. The predictor variables will be tested in separate models, both for the main outcome variable (BAI) and for the secondary outcome variable (SCL 90 R).

**Ethics and dissemination**

The study is approved by the Ethical Board, Department of Psychology, University of Copenhagen and by the Danish Data Protection Agency (OK308627) and personal data about the respondents are thus protected according to cf. section 50(1)(i) of the Danish Act on Processing of Personal Data. Moreover, the Danish Committee System on Health Research Ethics was informed of the project. The committee found that the project did not need separate ethical approval, since it does not include any biomedical intervention. Study findings will be disseminated through peer-reviewed publications and conference presentations.

**Author contributions**

SKKN and SV have primarily designed the study. IH, SD and KWT have contributed with analysis/research design input. SKKN wrote the first draft of this paper. All authors read, commented and approved the final paper.
Funding

The work is supported by Kristian Holt Hansen Foundation and Aase & Ejnar Danielsen Foundation.

Competing interests

None
References


30. WHO | International Classification of Diseases (ICD) WHO.

32. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders [Internet]. American Psychiatric Association; 2013


An investigation of general predictors for cognitive–behavioural therapy outcome for anxiety disorders in a routine clinical setting

Sara Kerstine Kaya Nielsen, Signe Vangkilde, Kate B Wolitzky-Taylor, Sarah Ingrid Franksdatter Daniel and Ida Hageman

*BMJ Open* 2016 6:
doi: 10.1136/bmjopen-2015-010898

Updated information and services can be found at:
http://bmjopen.bmj.com/content/6/3/e010898

These include:

**References**
This article cites 37 articles, 0 of which you can access for free at:
http://bmjopen.bmj.com/content/6/3/e010898#BIBL

**Open Access**
This is an Open Access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

**Email alerting service**
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

**Topic Collections**
Articles on similar topics can be found in the following collections

- Evidence based practice (734)
- Mental health (700)

**Notes**

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/