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Exploring Transdiagnostic Mechanisms of Change During Disorder-specific Cognitive Behavioural Therapy

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Abstract. The study aimed at exploring Intolerance of Uncertainty (IU) and Repetitive Negative Thinking (RNT) as possible mechanisms of change during disorder-specific Cognitive Behavioural Therapy in a natural clinical setting. RNT, IU and anxiety and depressive symptoms were assessed over time in a clinical sample (n=17) and in a student sample (n=38). In the clinical sample, the relationships between RNT, IU and symptoms were investigated with level, change, and mediation analysis. All variables declined over time in both groups. In the clinical sample, decline in IU and RNT were associated with decline of anxiety symptoms but not with decline of depressive symptoms. Decrease of IU mediated the relationship between decrease in RNT and decrease of anxiety symptoms.

Anxiety and mood disorders are highly prevalent worldwide (Howland & Thase, 2005; Kessler et al, 2003; Kessler et al., 2005). The disorders are associated with reduced quality of life (Angemeyer, Kilian, Wilms, & Wittmund, 2006; Cuijpers, Graaf, & van Dorsselaer, 2004; Mendlowicz & Stein, 2000; Rapaport, Cary, Fayyad, & Endicott, 2005) and substantial economic costs (Berto, D'Ilario, Ruffo, Di Virgilio, & Rizzo, 2000; Cuijpers et al., 2007; Greenberg & Birnbaum, 2005). Mental health professionals face the challenge to correctly assess and effectively treat these disorders.

The *ICD-10 Classification of Mental and Behavioural Disorders* (ICD-10) (World Health Organization, 1992) and the *Diagnostic and Statistical Manual of Mental Disorders* (DSM) (American Psychiatric Asssociation, 2013) are the most common systems of classification of mental disorders. These diagnostic manuals rely on the assumption that psychiatric disorders are distinct entities categorically differentiated from one another. Diagnosis is met when number of symptoms exceed a certain threshold level. The reliance on these diagnostic systems has contributed to high interrater reliability of psychiatric diagnosis (Brown, Campbell, Lehman, Grisham, & Mancill, 2001; Brown, DiNardo, Lehman, & Campell, 2001) which has enabled disorder-specific research and the development of empirically supported disorder-specific Cognitive Behavioural Therapy (CBT) treatment manuals (Barlow, Allen, & Choate, 2004). However, some argue that what has been gained in diagnostic reliability has come at the expense of diagnostic validity (Barlow et al., 2004).

Criticism of the current diagnostic systems include high comorbidity rates among the anxiety-and mood disorders and diagnostic overlaps. A considerable proportion of patients who seek treatment meet the criteria for more than one anxiety-and mood disorder, with point comorbidity rates as high as 55% and lifetime comorbidity rates of 76% (Brown & Barlow, 2009). Furthermore, the classification systems have been criticized for not clearly enough distinguishing one diagnosis from another. Boundary problems have been noted for instance in relation to generalized anxiety disorder (GAD) and mood disorders such as major depressive disorder (MDD) (Brown, Di Nardo, et al., 2001) and dysthymia (Brown & Barlow, 2009) as well as for diagnoses with overlapping features, such as panic disorder (PD) vs. panic disorder with agoraphobia (PDA) (Brown & Barlow, 2009). Disorder-specific CBT treatment protocols fail to directly treat comorbid and overlapping conditions.

The transdiagnostic approach offers an alternative way of understanding mental disorders. It suggests that the nature of mental disorders is not categorical (Brown & Barlow, 2009; van Praag, 2000). Instead, it stipulates that the diagnostic entities are more similar than different and have etiological commonalities (Harvey, 2004; Mansell, Harvey, Watkins, & Shafran, 2009). A clinical implication of the transdiagnostic approach is to target shared rather than disorder-specific features in therapy. Doing so has the potential to effectively accommodate comorbid and overlapping conditions.

A transdiagnostic etiological framework: the triple vulnerability model

For the anxiety and mood disorders, the shared etiological features have been summarized in a model referred to as "triple vulnerabilities" (Barlow, 2000, 2002). The model stipulates that anxiety and mood disorders emerge from the interaction of a general biological vulnerability, a general psychological vulnerability and a specific psychological vulnerability. The general biological vulnerability corresponds to core dimensions of temperament. The temperamental disposition to be easily aroused, reactive or nervous, known as neuroticism, is especially important in the development of anxiety and mood disorders (Brown & Naragon-Gainey, 2013; Suárez, Bennett, Goldstein, & Barlow, 2008). The general psychological vulnerability is a temporally stable sense of low perceived control over life events and emotions, developed from early childhood experiences resulting in inhibited coping strategies and self-efficacy, expressed as beliefs in one's inability to handle challenging and stressful events (Barlow, Ellard, Sauer-Zavala, Bullis, & Carl, 2014; Brown & Naragon-Gainey, 2013; Súarez et al., 2008) The two general vulnerabilities contribute to the clinical expression of frequent and intense psychological discomfort and negative evaluation of that discomfort. Put in other words, it increases the frequency and intensity of negative affect (NA) (Brown & Barlow, 2009). The specific psychological vulnerability is related to specific learning experiences and influence the focus of NA, meaning that different stimuli triggers NA for different patients. If NA reaches a certain threshold level, the patient may show different clinical expressions depending on the focus of NA. For instance, for patients with social anxiety disorder (SAD), the focus for NA is being socially evaluated. The focus for NA for patients with panic disorder or panic disorder with agoraphobia (PD/PDA) is intense emotions such as fear and associated bodily sensations (Barlow et al., 2004). For patients with OCD, the focus for NA is intrusive thoughts or images.

Maintaining factors of anxiety and mood disorders: avoidance strategies

Patients seek to avoid the unpleasant experience of NA by avoiding stimuli that triggers it. For instance, patients with SAD avoid social situations in attempt to avoid NA associated with being socially evaluated by others. Patients with PD/PA avoid intense bodily sensations, and patients with OCD avoid intrusive thoughts by engaging in compulsive behaviours and so on. Ironically, engaging in avoidance strategies tend to maintain distress in the long run (Barlow, 2014; Westbrook, Kennerley, & Kirk, 2011). This is because avoiding triggers of NA prevent corrective learning to take place. Craske (2014) argues that avoidance strategies prevent inhibitory learning. Patients who avoid distress-evoking situations never gain new memories that show that the stimuli is not indeed dangerous. Because of this, distress remains and future avoidance is likely. Another hypothesis is that cognitive avoidance prevents

corrective learning by inhibiting emotional processing of the feared stimuli (Foa & Kozak, 1986). The use of avoidance strategies is a common maintaining factor of distress that is found across diagnoses (Westbrook et al., 2001). Targeting avoidance strategies in CBT is an effective intervention, associated with symptom reduction and clinically significant improvements (Barlow, 2014).

Intolerance of Uncertainty - a transdiagnostic focus for negative affect

A focus for NA that is related to a range of anxiety and mood disorders is *Intolerance of Uncertainty* (IU). IU refers to "a dispositional characteristic that results from a set of negative beliefs about uncertainty and its implications" (Dugas et al., 2007). Experiencing uncertainty triggers negative affect. IU was initially regarded a specific psychological vulnerability for GAD (Dugas, Buhr & Ladouceur, 2004) but is also associated with MDD (Brown & Naragon-Gainey, 2013; Carleton et al., 2012; Yook, Kim, Suh, & Lee, 2010) and a range of other anxiety and mood disorders (Carleton et al., 2012; Gentes & Ruscio, 2011), including OCD (Tolin, Abramowitz, Brigidi, & Foa, 2003), SAD (Boelen & Reijntjes, 2009; Carleton, Collimore, & Asmundson, 2010), PA (Carleton et al., 2014), post traumatic stress disorder (PTSD) (Fetzner, Horswill, Boelen, & Carleton, 2013) and health anxiety disorder (HA) (Boelen & Carleton, 2012).

In a study aimed at investigating the triple vulnerability model using structural equation modelling, IU mediated the relationship between NA and GAD, SAD, MDD and obsessions/compulsion (Paulus, Talkovsky, Heggeness, Norton, 2015). In two studies using hierarchical regression analysis with data from many clinical patients with various anxiety disorders IU explained variance in all symptoms measures even after controlling for neuroticism (Mahoney & McEvoy, 2012; McEvoy & Mahoney, 2011). Furthermore, a large study comparing levels of IU in a clinical sample with patients diagnosed with a variety of anxiety disorders and depression (n=376) with levels of IU in a student and undergraduate sample indicated no difference in IU between person diagnosed with different anxiety disorders or depression, but all participants in the clinical group reported significantly higher IU compared to the community and undergraduate sample (Carleton et al., 2012).

A number of clinical studies show that levels of IU in clinical samples decrease following CBT-treatment and that this decrease is correlated with symptom reduction. For example, one study saw a significant decrease in levels of IU after treatment with a transdiagnostic CBT-protocol (Unified Protocol: Ellard, Fairholme, Boisseau, Farchione, & Barlow, 2010) in a clinical sample with patients diagnosed with different anxiety-and mood disorders (Boswell, Thompson-Hollands, Farchione, & Barlow, 2013). The decrease in IU was correlated to symptom reduction across diagnoses of GAD, SAD, PA, OCD and other anxiety disorders, and the relationship between change in IU and symptom severity at posttreatment was not disorder-specific (Boswell et al., 2013). Also, in a study on CBT group therapy for SAD, levels of IU decreased post-treatment as compared to pre-treatment, and the decreases were related to reductions in SAD symptoms (Mahoney & McEvoy, 2012b). In a study of transdiagnostic group CBT for anxiety, IU significantly decreased following treatment and predicted symptom reduction and clinical improvement across anxiety disorders (Talkovsky & Norton, 2016), leading the authors to conclude that IU appears to be an important transdiagnostic factor for treatment change.

Avoiding Uncertainty - Repetitive Negative Thinking

A covert avoidance strategy aiming at reducing NA related to uncertainty is the engagement in recurrent negative thinking. Recurrent negative thinking is a cognitive process that patients engage in to avoid NA and has mainly been investigated as worry and rumination. Worry is prevalent in most of the anxiety and mood disorder (de Jong-Meyer, Beck, & Riede, 2009), including GAD (Yook et al., 2010), SAD (Wells, & Carter, 2002), OCD (Rassin & Diepstraten, 2003), PA (Wells, & Carter, 2002), PTSD (Roussis, & Wells, 2008) and MDD (Yook et al., 2010). Rumination is elevated in depressed patients, predict the onset of depressive symptoms in non-depressed samples and contribute to the maintenance of depressive symptoms in people diagnosed with unipolar depression (Harvey, 2004). Rumination also predicts anxiety and is elevated in patients with OCD and PTSD (Harvey, 2004).

Research findings suggest that worry and rumination can be understood as minor variations of the same process (Ehring & Watkins, 2008). Using factor analysis, Ehring and Watkins (2008) concluded that when references to mood and future and past events respectively are removed, measures of worry and rumination essentially measures the same concept. Ehring and Watkins (2008) describes this thinking processes as "(a) *repetitive*, (b) *passive* and/or *relatively uncontrollable* and (c) *focused on negative content*." (Ehring & Watkins, 2008, p. 193.), and suggest the term Repetitive Negative Thinking (RNT) for this process. RNT is considered a transdiagnostic process (Drost et al., 2014; Harvey et al., 2009; McEvoy, Watson, Watkins, & Nathan, 2013). This assumption is supported by the fact that worry and rumination regularly co-occur in the same individual (Watkins, Moulds, & Mackintosh, 2005), measures of the respective constructs are highly correlated with each other (Fresco, Frankel, Mennin, Turk, & Heimberg, 2002; Harrington & Blankenship, 2002; Segerstrom, Tsao, Alden, & Craske, 2000), both worry and rumination are elevated across the anxiety-and mood disorders (Ehring and Watkins, 2008; Harvey, 2004) and predict anxiety and symptoms of depression prospectively in clinical (Drost, van der Does, van Hemert, Penninx, & Spinhoven, 2014; Harvey et al., 2009) and experimental settings (Ehring and Watkins, 2008).

The relationships between worry and rumination (although not conceptualised as RNT) and IU is well known (Buhr & Dugas, 2009; de Jong-Meyer et al., 2009). IU plays an important role in generating and maintaining worry (Buhr & Dugas, 2009; Carleton et al., 2012; Ladouceur, Gosselin, & Dugas, 2000; Yook e al., 2010), and is strongly related to rumination (de Jong-Meyer et al., 2009). IU has also been investigated as a mediator for reduction of worry during individual CBT treatment for patients diagnosed with GAD. Using mediation analysis, Bomyea et al. (2015) found that IU accounted for 59% of the reduction in worry during treatment.

The transdiagnostic approach suggest that the function of RNT is similar across the anxiety and mood disorders. More specifically, by engaging in RNT, patients avoid NA related to uncertainty. For example, a patient with GAD may regard processing a hypothetical future event verbally by thinking about possible scenarios and consequent actions a way of preparing for that future event. On the short term, this may lead to reductions of uncertainty. Making predictions about the future however will always be associated with a certain degree of uncertainty, why it is likely that NA is triggered again in a similar situation. A possible function of RNT in the given example is to avoid NA related to the uncertainty about what future holds in hand. By avoiding NA, corrective learning is prevented. Where IU is a transdiagnostic focus for NA, RNT is a transdiagnostic maintaining factor of IU. Reduction of RNT is associated

with symptom reduction across the anxiety and mood disorders (Drost et al., 2014) and has been suggested as a promising target for prevention of depression and anxiety disorders (Topper, Emmelkamp, & Ehring, 2010).

Intolerance of uncertainty and repetitive negative thinking as possible mechanism of change in disorder-specific CBT treatments

Disorder specific CBT treatment protocols have received considerable empirical support (Hofmann & Smits, 2008) and are recommended as psychotherapeutic treatment options for anxiety and mood disorders in Sweden and elsewhere (National Institute for Health and Care Excellence, 2009, 2014; Socialstyrelsen, 2016). The disorder-specific treatment protocols are designed to match the variations of various anxiety-and mood disorders, but share a common foundation. For example, all treatment protocols involve exposure exercises. Exposure interventions target maintaining factors of NA by targeting avoidance strategies. For instance, treatment manuals for PA involve interoceptive exposure (Barlow, 2014), whereas treatment protocols for OCD involve exposure and response prevention for obsessive thoughts or actions (Foa, Yadin, & Lichner, 2012) and behavioural activation for MDD involve breaking the avoidance pattern of passivity by getting back to daily routines and meaningful activities (Martell, Dimidjian, & Herma -Dunn, 2010). Although not commonly referred to as exposure, behavioural activation involves exposing the patient for triggers of NA, such as memories of loss. More recently, behavioural activation has been conceptualized as exposure, because it aims at breaking avoidance for NA (Barlow, 2013).

The fact that all CBT treatment protocols rely on exposure interventions aimed at reducing NA as a main component suggest that they may be quite similar. The transdiagnostic approach suggests that treatment effect may be mediated by transdiagnostic factors even in disorder-specific treatment manuals. Given their relevance in anxiety and mood disorders, IU and RNT are such potential transdiagnostic factors of therapeutic change.

Mapping mediators of therapeutic change. Although there is a general agreement that CBT is efficacious (Hofmann & Smits, 2008; National Institute for Health and Care Excellence 2009, 2014; Socialstyrelsen, 2016), less is known about *how* and *why* CBT produce therapeutic change. Understanding the processes by which therapeutic change occur is an important step toward further revision and improvement of CBT treatments (Doss, 2004; Kazdin, 2007).

The necessity of focusing on processes of therapeutic change in psychotherapy research has been outlined by Kazdin (2007). Rather than looking merely at the effects of treatment, one investigates what happens during treatment that affects the therapy outcome. This can be done by looking at mediators of change. A mediator of change is a variable that demonstrate important statistical relations between an intervention and outcome without necessarily explaining the exact process which causes change (Kazdin, 2007). Understanding the processes that account for therapeutic change can help optimize therapeutic change and improve treatments further (Doss, 2004; Kazdin, 2007).

In a review on mediators and mechanisms of change in psychotherapy research, Kazdin (2007) gives recommendations on how to conduct research studies on therapeutic change. The recommendations highlight using theory as a guide to which mediators to assess, to include measures of potential mediators in treatment studies, to establish a timeline of the suggested mediator and therapeutic outcome, to assess more than one mediator at a time, and to use study designs that can evaluate mediators (Kazdin, 2007). Kazdin (2007) especially emphasizes the benefits of study designs that assesses the proposed mediators and the outcome measures

several times during treatment. Such designs can evaluate whether changes in the mediator precede symptom change or vice versa, enabling causal interpretations.

In efficacy studies, usually conducted in research clinics, the efficacy of a treatment is investigated by comparing it with other available treatments (treatment as usual), to placebo conditions or to a wait-list control. An advantage of efficacy studies is high internal validity. It is possible to control variables such as therapist level of training, length of treatment, diagnostic homogeneity and access to a control group (Doss & Texas, 2006). However, findings from psychotherapy studies conducted in a controlled setting may lack external validity (Doss, 2004). Better generalizability and external validity can be achieved by conducting psychotherapy research in a natural clinical setting (Doss & Texas, 2006).

Studying mediators of change in a clinical setting. In many areas of clinical research in community settings, organizational and/or ethical considerations precludes study designs including no-treatment or wait-list controls (Doss & Texas, 2006). This means that they cannot compete with efficacy studies regarding internal validity. Doss and Texas (2006) argues that this does not necessarily mean that no serious interpretations of the finding can be made. With no control group, it is indeed impossible to make meaningful conclusions about the effects of a certain therapy on mediating and outcome variables. However, it is possible to examine correlates of change (Doss & Texas, 2006). Such study designs have potential usefulness as basis for future experimental studies (Doss, 2004; Doss & Texas, 2006). Also, studying the effectiveness of psychotherapy in a natural clinical setting has the advantage of generalizability and external validity. The result may mirror how the treatments are actually carried out, taken into account that therapists naturally have different level of training and experience, that patients may have comorbid conditions and that the length of therapy may vary. Because the results of effectiveness studies mirror the everyday use of treatment manuals, they have the potential to become clinically highly relevant and useful.

Although therapies stemming from the transdiagnostic approach are becoming increasingly investigated, few psychotherapy research studies have looked at transdiagnostic factors as potential mechanisms of change in disorder-specific CBT treatments. Such research studies conducted in a natural clinical setting are even rarer. Investigating potential mediators of transdiagnostic change in disorder specific CBT treatments in a natural clinical setting could contribute to increased knowledge about the processes of therapeutic change, enabling an effective treatment with the potential to better accommodate comorbid and overlapping conditions.

Aims and research questions. The aim of the present study is to explore RNT and IU as possible mechanisms of change during disorder-specific CBT in a natural clinical setting for patients with anxiety and mood disorders. Levels and change in RNT and IU and in outcome variables of anxiety and depressive symptoms will be assessed over time in a clinical sample and in a student sample. Another aim is to investigate the relationship between levels and change of RNT and IU and outcome variables, and whether late change in IU mediate the relationship between early change in RNT and late change in the outcome measures, as well as whether late change in RNT mediated the relationship between early change in IU and late change in the outcome measures. The main research questions are:

1. Are there differences between the clinical and student sample concerning the levels of and changes over time in: IU, RNT, anxiety symptom and depressive symptoms?
2. Are levels of IU related to outcome variables in a clinical sample?
3. Is change in IU related to change in outcome variables in a clinical sample?
4. Are levels of RNT related to outcome variables in a clinical sample?

5. Is change in RNT related to change in outcome variables in a clinical sample?
6. Are levels of and change over time in IU and RNT related in a clinical sample?
7. Does early change in RNT mediate the relationship between late change in IU and late change in outcome variables in a clinical sample?
8. Does early change in IU mediate the relationship between late change in RNT and late change in outcome variables in a clinical sample?

Method

Participants

Clinical sample. The clinical sample included 18 participants (13 women and 5 men. Ages 19-47, mean age 28.4; sd.=6.2) with different anxiety-and mood disorders. As principal diagnosis, three subjects had major depression (MDD), six had general anxiety disorder (GAD), three had social anxiety disorder (SAD), two had panic disorder (PA), two had obsessive compulsive disorder (OCD) and two had post-traumatic stress disorder (PTSD).

The number of comorbid diagnosis varied. Three subject met criteria for one diagnoses, 2 subjects had two diagnoses, 5 had three diagnoses, 5 had four diagnoses, one had 6 diagnoses and 2 subjects had seven diagnoses.

The level of education varied. 12 subjects had university education, 2 had upper secondary school, 2 had community college and 2 did not say.

Because of a small positive skewness in the data distribution, one outlier was removed to alleviate the skewness, leaving 17 participants for data analysis. The outlier was removed per standard deviation based rules (Field, 2009), meaning that values further away from the mean than 2.5 standard deviations are removed.

Data loss. Initially, 45 patients agreed to participate in the study. 27 participants (60%) were excluded from the study. Of those, 7 did not meet inclusion criteria and 11 were excluded due to discontinuation of treatment or because they stopped responding to self-report measures. Another 9 subject were excluded from data analysis because they had not responded to the self-report measures at the first three consecutive points of measurement. There is no information about how many of those asked to participate in the study chose not to.

Due to the big internal data loss from the clinical sample, the analysis of the data took a slightly different course than planned. 27 participants from the clinical sample were eligible for the study and responded to the self-report measures during treatment, but not everyone did so every fourth week. The analysis was therefore conducted on data from the first three points of measurement only, corresponding to week 1, 4 and 8 of treatment. From those points of measurement, data from 18 participants were available. Of those 18, 9 had terminated treatment and 9 were still in therapy. Data from the corresponding points of measurement for the student sample was analysed.

Student sample. The student sample consisted of undergraduate- and graduate students at University of Gothenburg and Chalmers University of Technology. The sample included 41 subjects (22 women and 19 men in ages 19-43, mean age 24.1 years; s.d.=6.0) studying psychology (n=13), nursing (n=6), engineering (n=20) and physiotherapy (n=2). Because of a small negative skewness in the data distribution, three outliers were removed from the data

analysis, leaving 38 subjects for data analysis to alleviate the skewness. Outliers were removed per standard deviation based rules (Field, 2009).

Measures

Diagnostic Interview. The *MINI-International Neuropsychiatric Interview (M.I.N.I)* (Van Vliet & De Beurs, 2006) is a structured diagnostic interview used in assessment of diagnosis according to DSM and ICD-10 criteria. In the present study M.I.N.I version 7.01 was used which covers diagnosis in the latest version of DSM (DSM-5). It covers the most important axis 1-diagnosis, for example depressive disorders, anxiety disorders, eating disorders and substance-related and addictive disorders. It was developed to be briefer than other diagnostic interviews and takes about 15-20 minutes to administer. When developing the instrument, validity and reliability was studied by comparing the M.I.N.I to other diagnostic interviews (SCID-P and CIDI). In comparison to SCID-P and to CIDI, the M.I.N.I demonstrated overall acceptable validity. The interrater reliability for most diagnoses were excellent. The test-retest reliability was good for most of the diagnoses (Sheehan et al., 1998).

Intolerance of Uncertainty. *The Intolerance of Uncertainty Scale Short Form (IUS-12)* measures negative beliefs about and reactions to uncertainty. It is a 12-item version of the original 27-item Intolerance of Uncertainty Scale (IUS) (Buhr & Dugas, 2002). The maximum total score is 60. IUS-12 has shown content, convergent, criterion and discriminant validity in multiple populations (Buhr & Dugas, 2002, 2006; Carleton, Norton, & Asmundson, 2007). The test-retest reliability (r =.74) and internal consistency (α=.94) are acceptable and excellent respectively (Buhr & Dugas, 2002). The 12-item version is highly correlated (r = .96) with the full version in undergraduate (Carleton et al., 2007; Khawaja & Yu, 2010) and clinical samples (McEvoy & Mahoney, 2011). The IUS-12 consists of two subscales, measuring prospective anxiety about uncertainty (e.g., "I always want to know what the future has in store for me.") and inhibition of action due to uncertainty (e.g., "When it's time to act, uncertainty paralyses me."). Since no prior hypothesis relating to each subscale was present in this study, the total score was used. To fit the Swedish population, a back-translation procedure was performed involving the author and a native English speaking licensed psychologist. Divergences in translation were resolved through consensus.

Repetitive Negative Thinking. The *Perseverative Thinking Questionnaire (PTQ) (*Ehring et al, 2011) is a questionnaire designed to measure RNT independently of content or disorder, hence allowing transdiagnostic comparisons. The PTQ consists of 15-items and measures one higher-order factor representing RNT in general and three lower-order factors representing (1) the core characteristics of RNT (repetitiveness, intrusiveness, difficulties with disengagement), (2) perceived unproductiveness of RNT and (3) RNT capturing mental capacity. Each characteristic is measured by three items, for example 'my thoughts prevent me from focusing on other things' for measuring the extent of capturing mental capacity, and 'the same thoughts keep coming back to my mind again and again' for repetitiveness. The maximum total score is 60. For the English version of PTQ, the internal consistency is excellent ($\boldsymbol{\alpha}$=0.95) for the total score and good to excellent for all subscales ($\boldsymbol{\alpha}$ = 0.83-0.94). The PTQ has good convergent, construct and - criterion validity (Ehring et al., 2011) as measured by associations with concurrent levels of anxiety and depression and prospective levels of depression. Since no prior hypothesis relating to each subscale was present in this study, the total score was used. To fit the Swedish population, a back-translation procedure was

performed involving the author and a native English speaking licensed psychologist. Divergences in translation were resolved through consensus.

Anxiety severity. *The Generalized Anxiety Disorder Scale (GAD-7)* is a 7-item measure initially designed to identify the presence of and measure severity of GAD (Spitzer, Kroenke, Williams, & Löwe, 2006). It is however also commonly used as a measure of general anxiety symptoms in clinical populations of various anxiety and mood disorders and can be used to detect change of anxiety symptoms in such heterogeneous samples (Beard & Björgvinsson, 2014). Respondent are asked to assess how often during the past two weeks they've been bother by symptoms such as "feeling nervous, anxious or on edge?" and "not being able to stop or control worrying?". The maximum score is 21. Internal consistency and convergent validity is good for populations of varied anxiety and mood disorders. In the present study, the Swedish version of GAD-7 was used to measure change of anxiety symptoms over time transdiagnostically.

Depressive symptoms. The *PHQ-9* is a 9-item module covering symptoms of depression, derived from the more extensive Patient Health Questionnaire (PHQ) covering 8 different DSM-IV diagnoses (Kroenke, Spitzer, & Williams, 2001). PHQ-9 can be used to screen for MDD, but the measure is also sensitive to other types of depression and depressed mood, and to severity of the conditions. In the present study, PHQ-9 was used to transdiagnostically measure change of depressive symptoms over time. Each of the 9 items can be scored from 0 (not at all) to 3 (nearly every day) meaning that the total score can range from 0-27. The internal consistency of the English version of PHQ-9 (α = 0.86-0.89) and re-test reliability (α = 0.84) has shown to be good to excellent in clinical samples (Kroenke et al, 2001). In the present study, the Swedish version of PHQ-9 was used.

Procedure

Recruitment process. Patients were recruited between March 2016 and December 2016 from an outpatient psychiatric clinic in Gothenburg specialized in CBT treatments. At intake, psychologists and practicing physicians informed about the study and written informed consent was obtained. In agreeing to participate, patients agreed to respond to monthly self-report measures during their treatment. Also, they permitted the author to access de-identified demographic variables obtained from patient's journals.

Patients were eligible for participation if diagnosed with at least one of the following disorders: MDD, PD, PDA, agoraphobia (A), social anxiety disorder (specific and generalized) (SAD), GAD, HA, PTSD and OCD. Only patients who were offered and agreed on CBT-treatment for their principal diagnosis were eligible to participate. Comorbid conditions among the disorders did not exclude participation in the study. However, patients who received medical treatment with benzodiazepines and patients who had previously completed CBT-treatment at the clinic were excluded from participation.

Assessment. All patients followed the existing procedure of assessment at the clinic and were diagnosed by a clinical psychologist or psychiatrist. The assessment procedure involved completing the MINI-interview and a battery of self-report measures. For the study, patients completed an additional series of self-report measurements including IUS-12, PTQ, GAD-7 and PHQ-9. The measures were administered at intake (pre-treatment) and every fourth week during therapy up to therapy termination. All self-report measures were administered using an online survey instrument enabling patients to respond at home using a computer. Patients could also choose to use a computer at the clinic. The patients had a 4-day span to complete the

measurements, and clinicians routinely reminded patients to respond. The time between pre-treatment and start of treatment varied between 2 to 4 weeks.

Because only very few participants responded to the self-report measures at pre-treatment, this data was not assessed.

Treatment. All patients received disorder-specific manualized CBT-treatment for their principal diagnosis.

In total, six different treatment protocols were included within the scope of the study. *Behavioural Activation* (Martell et al, 2010) was used to treat MDD, *Prolonged Exposure Therapy* (Foa, Hembree, & Rothbaum, 2007) to treat PTSD, *Intolerance of Uncertainty Therapy* (Robichaud & Dugas, 2006) to treat GAD, *Exposure and Response Prevention* (Foa, Yadin, & Lichner, 2012) to treat OCD, *Social Phobia Treatment* (Clark, 1997) to treat SAD, Barlow's *Panic Control Treatment for Panic Disorder* (Barlow, 2014) to treat PD and PDA and *Furer and Walker's CBT Treatment* (Furer, Walker, & Stein, 2010) to treat HA. Although presenting unique components, all treatment protocols include elements of exposure.

The treatments were carried out by licensed clinical psychologists at the clinic. The therapists were experienced and trained in CBT, but received no special training for the study. As a routine to ensure treatment integrity, therapists at the clinic receive supervision by a senior licensed psychologist responsible for scientific adherence and competence. More specifically, when employed all therapist receive feedback on videotaped sessions and patient's journals to ensure adherence to treatment protocols. Hence, a certain amount of internal validity is retained.

Because only 9 participants had completed treatment within the data collection period, data from the 9 participants still under treatment was included in the analysis. For those who had completed treatment, the length of treatment varied between 9 and 21 weeks, with an average of 14,8 weeks. Those who were still under treatment had, at the time of final data collection, completed between 9 and 30 weeks of treatment with an average of 21,1 weeks

The student sample. The student sample was recruited between May and June 2016 from different university courses after visiting one of their classes. Informed written consent was obtained after a brief description of the study. In agreeing to participate, subjects consented to reply to a series of self-report measurements administered via email regarding psychological health every fourth week during a five-month period. The student sample received the same series of measurements as the clinical sample, namely IUS-12, PTQ, GAD-7 and PHQ-9. The first series of measurements was administered using paper and pen when visiting their classes. The following four measurements were administered via email using an online survey instrument. The student sample did not receive any diagnostic assessment. Instead, they were asked if they currently had any contact with health care facilities regarding their psychological health, if they currently were engaged in medical or psychological treatment at an outpatient psychiatric clinic, or if they had ever been in contact with outpatient or inpatient psychiatric care regarding their psychological health. After termination of the data collection, all subjects were asked if they had started medical or psychological treatment during the data collection period. Respondents who were engaged in treatment before or started treatment during data collection were excluded from participation. As in the clinical sample, data from the first three points of measurements were analysed. Subjects did not receive any payment for participating in the study, but were offered a copy of the study when finished.

Data analysis

Changes in levels of IU, RNT, GAD-7 and PHQ-9 across measurement points in the clinical and student sample respectively were analysed using mixed repeated measure ANOVA for each variable. The ANOVA also assessed whether there were any differences in levels and/or change of scores of IU, RNT, GAD-7 and PHQ-9 between the clinical and student sample.

To investigate relationships between IUS-12 and PTQ and symptom measures respectively at the different points of measurement, multiple bivariate product moment correlations were conducted. Bivariate product moment correlations were also used to investigate the relationships between IUS-12 and PTQ at the different points of measurement. The strength of the relationships was established using Cohen's (1992) guidelines, where .10 is a small effect, .30 a medium effect and .50 a large effect.

To investigate whether the changes of IU, RNT, GAD-7 and PHQ-9 across the measurement points correlated with each other in the clinical sample, bivariate product moment correlations were calculated on change scores. The strength of the relationships was established using Cohen's (1992) guidelines, where .10 is a small effect, .30 a medium effect and .50 a large effect. Individual change scores were calculated manually by subtracting the score of each variable from one point of measurement from the score of the corresponding variable in the previous point of measurement. Mean change scores were then calculated. Mean change scores representing changes in the variables between the second and first point of measurement are referred to as early change. Mean change scores representing changes in the variables between the third and second point of measurement are referred to as late change.

Mediation analysis (Hayes, 2009) using the SPSS macro PROCESS tested whether the effect of IU on the outcome measures was mediated by change in RNT, and whether the effect of RNT on the outcome measures was mediated by changes in IU in the clinical sample. Specifically, two mediation analysis tested whether the effect of early change in RNT on late change in GAD-7 and PHQ-9 respectively was mediated by late change in IUS-12. Two mediation analysis tested whether the effect of early change in RNT on late change in GAD-7 and PHQ-9 was mediated by late change in RNT. Mediation analysis assesses whether the relationship between a predictor variable and an outcome can be explained by their relationship to a third variable, a mediator (Hayes, 2009).

Result

Levels and change across time in the clinical and student sample

The means and standard deviations of IUS-12, PTQ, GAD-7 and PHQ-9 were assessed at three points of measurement in the clinical and student sample. The first point of measurement was at week 1, the second point of measurement was at week 4 and the third measurement was at week 8. Mixed ANOVA repeated measures were used to assess main effect of change across the measurement points and to see if there was an interaction effect between group and change. Between-subject effect from the mixed ANOVA indicated whether the groups differed in their scores of IUS-12, PTQ, GAD-7 and PHQ-9. See table 1 for detailed descriptive statistics.

Table 1

Means and (standard deviations) of IUS-12, PTQ, GAD-7 and PHQ-9 in the student sample (n=38) and in the clinical sample (n=17). The main – and interaction effect of change across measurement point 1 (M1), measurement point 2 (M2) and measurement point 3 (M3) is illustrated with F- value and effect size (η_p^2 .)

	Student sample (*n*=38)			Clinical sample (*n*=17)			Main effect		Interaction-effect	
	M1	M2	M3	M1	M2	M3				
	M (*Sd.*)	*M* (*Sd.*)	*M* (*Sd.*)	*M* (*Sd.*)	*M* (*Sd.*)	*M* (*Sd.*)	*F*	η_p^2	*F*	η_p^2
IUS-12	25.8 (7.4)	25.4 (7.0)	23.9 (7.9)	42.6 (8.1)	39.5 (12.2)	37.7 (11.0)	12.95***	.20	3.03	.05
PTQ	22.1 (10.6)	21.9 (10.9)	19.5 (11.5)	40.0 (10.0)	39.1 (10.6)	36.0 (13.2)	7.12*	.19	.28	.01
GAD-7	4.6 (4.0)	3.5 (2.4)	2.5 (2.7)	12.3 (4.6)	9.9 (4.1)	10.2 (4.5)	9.25***	.15	.09	.02
PHQ-9	5.3 (4.6)	4.4 (4.3)	3.8 (3.6)	12.5 (6.3)	11.4 (5.8)	10.0 (5.3)	5.82**	.10	.54	.01

*$p < .05$; ** $p < .01$; ***$p < .001$ per mixed ANOVA repeated measures design

IUS-12. The main effect for IUS-12 was significant, meaning that there was a significant decrease of IUS-12 in both groups over time. The interaction-effect between group and time was however not significant, showing that the groups did not differ in terms of change. There was a significant effect of group, indicating that ratings of IUS-12 from the clinical and student sample were different. The clinical sample scored higher on IUS-12 than the student sample did over time.

PTQ. Mauchly's test indicated that the assumption of sphericity had been violated, $\chi^2(2) = 6.926$, $p = .03$, therefore degrees of freedom were corrected using Huynh-Feldt estimates of sphericity ($\varepsilon = .94$). The result show that the main effect for PTQ was significant, meaning that both groups reported a significant decline in PTQ over time. The interaction-effect between group and time was however not significant, showing that the groups did not differ in terms of change. There was a significant effect of group, indicating that ratings of PTQ from the clinical and student sample were different. The clinical sample scored higher on PTQ than the student sample across all measurement points.

GAD-7. The main effect for GAD-7 was significant, meaning that there was a significant decrease of GAD-7 in both groups over time. The interaction-effect between group and time was however not significant, showing that the groups did not differ in terms of change. There was a significant effect of group, indicating that ratings of GAD-7 from the clinical and student sample were different. The clinical sample scored higher on GAD-7 than the student sample across all measurement points.

PHQ-9. The main effect for PHQ-9 was significant, meaning that there was a significant decrease of PHQ-9 in both groups over time. The interaction-effect between group and time was however not significant, showing that the groups did not differ in terms of change. There was a significant effect of group, indicating that ratings of PHQ-9 from the clinical and student sample were different. The clinical sample scored higher on PHQ-9 than the student sample across all measurement points.

Relationships among IUS-12, PTQ and symptom measures in the clinical sample at three points of measurement: level analysis

Bivariate product moment correlations were conducted to assess the relationship between IUS-12 and RNT, and the relationship between IUS-12 and RNT and outcome measures respectively. These correlations were assessed at first, second and third point of measurement in the clinical sample (*n*=17). See table 2.

Table 2

Product moment correlations (r) of levels of IUS-12, PTQ, GAD-7 and PHQ-9 at first point of measurement (M1), second point of measurement (M2) and third point of measurement (M3) in the clinical sample (n=17).

	IUS-12			PTQ			GAD-7			PHQ-9		
	MI	M2	M3	M1	M2	M3	M1	M2	M3	M1	M2	M3
M1 IUS-12	1.00											
M2 IUS-12	.89**	1.00										
M3 IUS-12	.79**	.87**	1.00									
M1 PTQ	.86**	.79**	.85**	1.00								
M2 PTQ	.84**	.78**	.72**	.96**	1.00							
M3 PTQ	.72**	.69**	.79**	.89**	.90**	1.00						

Table 2 continues on the next page.

Table 2 continued.

M1 GAD-7	.54**	.33	.38	.65**	.67**	.60*	1.00					
M2 GAD-7	.57*	.53*	.45	.59*	.66**	.51*	.72**	1.00				
M3 GAD-7	.47	.38	.64**	.70**	.63**	.74**	.77**	.47	1.00			
M1 PHQ-9	.58*	.45	.49*	.70**	.70**	.52*	.71**	.61**	.67**	1.00		
M2 PHQ-9	.54*	.48	.48	.64**	.72**	.61**	.56**	.73**	.53*	.70**	1.00	
M3 PHQ-9	.41	.36	.48*	.47	.90**	.52*	.50*	.41	.74**	.56*	.66**	1.00

*$p < .05$;**$p < .01$ (two-tailed)

Relationship between IUS-12 and the symptom measures. The relationship between levels of IUS-12 and levels of GAD-7 was significant at all points of measurement, indicating medium to large effects (Cohen, 1992). The relationship between levels of IUS-12 and levels of PHQ-9 was significant at all points of measurement except the second, indicating medium effects (Cohen, 1992).

Relationship between PTQ and the symptom measures. The relationship between levels of PTQ and levels of GAD-7 was significant at all points of measurement, indicating large effects (Cohen, 1992). The relationship between PTQ and PHQ-9 was also significant at all points of measurements, indicating medium to large effects (Cohen, 1992).

Relationship between IUS-12 and PTQ. At all points of measurement, PTQ and IUS-12 were correlated with each other, indicating large effects (Cohen, 1992).

Change analysis in the clinical sample

Bivariate product moment correlations on change scores were conducted to assess whether changes in IUS-12, PTQ, PHQ-9 and GAD-7 correlated. Change scores representing changes in the variables between the second and first point of measurement are referred to as early change. Change scores representing changes in the variables between the third and second point of measurement are referred to as late change. Total change represents the changes in the variables between the third and first point of measurement. See table 3.

Table 3

Product moment correlations (r) of early change (E.C), late change (L.C) and total change (T.C) in IUS-12, PTQ, GAD-7 and PHQ-9 in the clinical sample (n=17).

	IUS-12			PTQ			GAD-7			PHQ-9		
	E.C	L.C	TC	E.C	L.C	T.C	E.C	L.C	T.C	E.C	L.C	T.C
E.C IUS-12	1.00											
L.C IUS-12	-.38	1.00										
T.C IUS-12	.57*	.55*	1.00									
E.C PTQ	.09	-.50*	-.36	1.00								
L.C PTQ	.18	-.42	.53*	-.07	1.00							
T.C PTQ	.20	.16	.33	.39	.90**	1.00						
E.C GAD-7	.45	-.34	.11	.19	-.27	-.16	1.00					
L.C GAD-7	-.15	.65**	.44	-.49*	.58*	.32	-.72**	1.00				
T.C GAD-7	.27	.56*	.74**	-.49*	.55*	.28	.03	.68**	1.00			
E.C PHQ-9	.14	-.13	.01	.39	.10	.27	.58*	.09	.01	1.00		
L.C PHQ-9	-.10	.31	.18	-.33	.26	.09	-.38	.61	.48	-.30	1.00	
T.C PHQ-9	.01	.19	.18	-.01	.32	.29	.09	.25	.45	.06	.70**	1.00

*$p < .05$; **$p < .01$ (two.-tailed).

Correlations of change in IUS-12 and change in the outcome measures. There was a significant relation between total change in IUS-12 and total change in GAD-7. Late change in IUS-12 was significantly related to late change in GAD-7 and to total change in GAD-7. All the significant relationships indicated large effects (Cohen, 1992). The relationship between total change in IUS-12 and total change in PHQ-9 was not significant.

Correlations of change in PTQ and change in the outcome measures. Early change in PTQ was significantly related to late change in GAD-7, and to total change in GAD-7, indicating medium to large effects (Cohen, 1992). There was no significant relationship between total change in PTQ and total change in PHQ-9. There was a significant relationship between late change in PTQ and late change in GAD-7, and to total change in GAD-7, indicating medium to large effects (Cohen, 1992).

Correlations of change in IUS-12 and change in PTQ. There was a significant relationship between early change in PTQ and late change in IUS-12, indicating a large effect (Cohen, 1992). There was also a significant relationship between total change in IUS-12 and late change in PTQ, a large effect (Cohen, 1992). There was no significant relationship between early change in IUS-12 and late change in PTQ. There was no significant relationship between total change in PTQ and total change in IUS-12. There was no significant relationship between late change in PTQ and late change in IUS-12.

Mediation analysis of change

A mediation analysis was performed using the SPSS macro PROCESS to examine whether the effect of early change in PTQ on late change in GAD-7 was mediated by late change in IUS-12. Bootstrapping based on 5000 samples was used to obtain confidence limits for indirect effects. There was a significant indirect effect of early change in PTQ and late change in GAD-7 through late change in IUS-12, b = .41, BCa CI [-1.56, -.02]. This represents a relatively small effect, partially standardized indirect effect = -.09, 95% BCa CI [-.30, -.00]. The mediation analysis shows that late change in IUS-12 mediated the effect of early change in PTQ and late change in GAD-7.

Because there was no significant correlation between early change in PTQ and late change in PHQ-9, no mediation analysis was performed to assess late change in IUS-12 as potential mediator of that change. Hence, research question 18 is left unanswered.

Similarly, since no significant correlation between early change in IUS-12 and late change in GAD-7 or late change in PHQ-9 was noted, no mediation analyses were conducted to examine whether late change in RNT mediated the effect of early change in IUS-12 and the respective outcome measures. Hence, research questions number 19 and 20 are left unanswered.

Discussion

The aim of the present study was to explore RNT and IU as possible mechanisms of change during disorder-specific CBT in a natural clinical setting for patients with anxiety and mood disorders. Levels and change in RNT and IU and in outcome variables of anxiety and depressive symptoms were assessed over time in a clinical sample and in a student sample. Another aim was to investigate the relationship between levels and change of RNT and IU and outcome variables, and whether late change in IU mediate the relationship between early change in RNT and late change in the outcome measures, as well as whether late change in RNT mediated the relationship between early change in IU and late change in the outcome measures.

The results showed that levels of IU, RNT and symptoms of anxiety and depression were elevated for patients with MDD, GAD, SAD, PA, OCD and PTSD as compared to in a healthy student sample. This in in line with previous research showing associations between IU and GAD (Dugas et al., 2004), MDD (Brown & Naragon-Gainey, 2013; Carleton et al, 2012; Yook et al., 2009), SAD (Boelen & Reijnties, 2009; Carleton et al., 2010), PA (Carleton et al., 2014), OCD (Tolin et al., 2003) and PTSD (Fetzner et al., 2013). It has been noted before that levels of IU were higher in a heterogeneous clinical sample as compared to in student sample (Carleton et al, 2012). In sum, the results from the present study may be interpreted as supporting the thesis that IU is a transdiagnostic factor.

That RNT was elevated for patients in the heterogeneous clinical sample as compared to in the student sample can be interpreted as supporting the claim (Drost et al, 2014; Ehring & Watkins, 2008;McEvoy et al., 2013) that RNT is a transdiagnostic factor. Previous research has shown elevated levels of recurrent negative thinking conceptualised as worry and rumination in anxiety and mood disorders (Harvey, 2004). The findings from the present study suggest that elevated levels of negative repetitive thinking conceptualised as variations of the same process is too. Therefore, it seems like RNT is a clinically relevant concept that could be investigated further.

Findings from the present study also showed that levels of IU and RNT and symptom measures declined during 8 weeks of disorder-specific CBT treatment in the clinical sample. Unexpectedly, this decline was however not significantly different from the decline in the variables in the student sample. This finding can be interpreted in several ways. A possible explanation for this is that changes in RNT, IU and symptom measures occur at a later stage of therapy. Unfortunately, this could not be investigated in the present study because only changes during the first 8 weeks of therapy was investigated due to the big internal data loss. The first part of treatment is about forming a therapeutic alliance, gathering information about the patient's problems, doing behaviour analysis and psychoeducation. During this early stage, patients usually experience ease of symptoms partly due to increased hope and positive expectations of the treatment. It is possible that such factors decreased the number of symptoms and IU and RNT between the first and second point of measurement in the present study. Exposure exercises usually start at a later stage of treatment, and although they aim at reducing NA and avoidance, which would predate reduction of RNT and consequently IU, this effect is usually seen later in therapy. Instead, it has been noted before that exposure modules are associated with a temporary increase of symptoms. It is possible that the second and third point of measurement mirrored such an effect, which is a possible explanation for why the decrease of IU, RNT and symptoms between the second and third point of treatment was not very big. If the data set had allowed analysis from more points of measurement, and especially from entire treatments, it is possible that the decline would have been bigger.

The results showed no significant difference of change in the proposed mechanisms of change and symptoms in the clinical and student sample. At first glance, this could be interpreted as there was no treatment effect. However, the effort to examine treatment effect by comparing changes in symptom measures in a clinical sample receiving treatment to a student sample not receiving treatment has its limitations. For one thing, the groups had an initial big difference in levels of symptoms. Although this was expected, it could have meant that changes in the variables in over time, although not significantly different in levels, may have been qualitatively different. It is possible that changes in the student sample reflected subclinical variations rather than indicating that the participants went from clinically relevant levels of symptoms to subclinical levels. The changes in the clinical sample however may pose clinical relevance in the sense that subjects went from more severe symptom levels to less

severe symptoms, marking a clinically relevant decrease. The present study did not investigate the clinical implications of the decline of IU, RNT and symptom measures in the clinical sample, but such investigation could be an interesting focus for future research studies. Based on the result from the present study, it cannot be concluded weather the fact that the groups did not differ in terms of change had anything to do with actual treatment effect.

The present study also aimed at investigating the relationship between IU and RNT in a clinical sample. The results reflected large point correlations at every point of measurement. This may be interpreted as IU and RNT being closely associated and co-occuring in the same individuals over time. Previous research has shown the relationship between IU and worry and rumination respectively (Buhr & Dugas, 2009; de Jong-Meyer et al., 2009), but not when conceptualised as variations of the same process. Therefore, the finding from the present study may add to the transdiagnostic field by showing the potential clinical utility of RNT. However, the findings of correlations do not say anything about the clinical relevance of the relationship. In other words, it cannot be concluded whether high IU leads to high RNT or the other way around. The change analysis however opens for more extensive conclusions.

The change analysis indicated that there was no significant relationship between early change in IU and late change in RNT. This effect is opposite from what was expected based on the assumption that RNT is an avoidance strategy for NA associated with uncertainty. Theoretically, the need to avoid uncertainty would decrease as patients become more tolerant of uncertainty. The non-significant effect as noted in the change analysis can be understood in several different ways. For example, the Swedish version of PTQ could be a poor estimate of RNT, perhaps having worse psychometric properties than the original version. Also, it may be that other, not investigated avoidance strategies were more important avoidance strategies in the clinical sample. Another possibility is that the data analysis failed to detect an actual effect in the population.

The change analysis also noted a significant negative relationship between early change in PTQ and late change in IUS-12, indicating that as when patients engaged less in RNT, they became *more* intolerant of uncertainty. This effect was not expected. If anything, it would be more likely that IU would decrease following a reduction of RNT. However, the present findings suggest differently. One way to understand this is in relation to the stage of therapy this effect was noted in. The late change in IU could have corresponded to exposure modules in therapy. If patients did not engage in RNT as much as they had done before when exposed for NA, they had no way of "handling" the uncertainty they were exposed of, which could lead to increased uncertainty. It is also possible that the observed effect did not mirror an actual relationship but rather limitations in the data analysis. The inconsistent findings about the relationship between changes in IU and changes in RNT suggest future research on the subject.

Another aim of the present study was to explore the relationship between change in IU and change in anxiety and depressive symptoms for patients with anxiety-and mood disorders. Change analysis showed a significant relationship between change in IU and change in general anxiety symptoms during treatment. This is in line with previous research from transdiagnostic group treatment for anxiety disorders (Talkovsky & Norton, 2016), in which decrease in IU correlated with decrease of anxiety symptoms. Also, decrease in IU during transdiagnostic treatment have been associated with decrease of symptoms for patients with different anxiety and mood disorders (Boswell et al., 2013). That this effect was found in disorder-specific CBT-treatments is noteworthy. The finding may reflect a process of how therapeutic change comes about, marking an important step for future revision of CBT-treatments. Because changes in IU seem important for reduction of anxiety symptoms across particular disorders, targeting IU more directly may be an effective treatment intervention. Also, it may leave clinicians better

prepared to treat comorbid and overlapping conditions. However, although the clinical sample in the present study included patients with various anxiety and mood disorders, 6 out of 17 (35 %) had GAD. It is possible that this could have affected the correlation between measures of IU and GAD-7, as GAD-7 was initially designed to measure levels of GAD in particular.

Change analysis indicated that there was no significant relationship between changes in IU and changes in depressive symptoms transdiagnostically. This could be interpreted in several ways. One possibility is that IU is more related to anxiety symptoms than depressive symptoms. Previous research based on larger sample sizes shows differently (Brown & Naragon-Gainey, 2013; Carleton et al., 2012; Paulus, Talkovsky, Heggeness, & Norton, 2015; Yook et al., 2009) though. In the present study, it is possible that the diagnostic composition of the clinical group influenced the results, as most patients had anxiety disorders rather than mood disorders. Also, although not significant, the relationship between total change in IUS-12 and PHQ-9 was strong and marked a trend. Given the small sample size and problem related to statistical power, it is possible that the change analysis simply did not catch an actual effect in the population. An interesting focus for further investigation would be to investigate the relationship between IU and depressive symptoms in a bigger clinical sample with various anxiety-and mood disorders.

The relationships between change in RNT and change in the symptoms measures were also assessed in the present study. The results show that total change in RNT was correlated with total change in GAD-7 but not to total change in PHQ-9. In other words, IU and RNT seem to have similar relationships to GAD-7 and PHQ-9. An interpretation of this is that patients with a decrease in avoidance of NA related to uncertainty are less anxious but not less depressive. This could indicate that RNT is more related to anxious symptoms than to depressive ones. This does not however necessarily mean that RNT is not a transdiagnostic process, given that patients across the anxiety and mood disorders present both anxious and depressive symptoms. The result could however reflect the diagnostic composition in the clinical sample. Most the patients had anxiety disorders rather than mood disorder, possibly meaning that changes in anxiety symptoms were greater in the clinical sample than changes in depressive symptoms.

A mediation analysis assessed whether the relationship between early change in RNT and late change in anxiety symptoms was mediated by late change in IU. In other words, it was investigated whether decline of RNT predated decline of IU which related to decrease of anxiety symptoms. The results indicated that such an effect was present. This is an interesting finding. It supports previous claims that RNT (Topper et al., 2010) and IU (Talkovsky & Norton, 2016) are important factors for treatment change. The finding from the present study may reflect that as patient stop avoiding NA related to uncertainty, they become more tolerant of uncertainty which correlates with a decrease of anxiety symptoms. This could be a clinically relevant finding, suggesting that targeting RNT is an effective treatment intervention transdiagnostically.

In conclusion, the present study has contributed to the clinical field by supporting previous research showing that IU and RNT are correlated to anxiety and depressive symptoms for patients with various anxiety and mood disorders. The results support previous transdiagnostic research showing that levels of both IU and RNT are higher in a clinical sample than in a student sample, and by showing that the constructs are strongly related in a clinical sample. Also, in both a clinical sample and a student sample, IU, RNT and symptoms of anxiety and depression decreased over time. In the clinical sample, decreases in IU and RNT were correlated with decrease of anxiety symptoms but not to decrease of depressive symptoms. Furthermore, the relationship between early change in RNT and later change in anxiety

symptoms was mediated by a late change in IU, which could indicate that patients become more tolerant of uncertainty as they engage less in RNT, which in turn is correlated to reduction of anxiety symptoms.

Limitations

The results in the present study are based on small sample sizes which has affected the chances to find statistically significant associations and draw meaningful conclusions as well as increased the risk of type-I errors. The limited number of participants in the clinical sample meant that strong correlations were needed for statistical significance. For example, based on the assumption that RNT is an avoidance strategy for IU, it was expected that RNT would decrease following reduction of IU. The correlation between early change in in IUS-12 and late change in PTQ was however not significant, although presenting an effect size of $r = .18$, which is usually regarded a small to medium effect (Cohen, 1992). Also, the relationship between late change in PTQ and late change in GAD-7 was not significant, although its effect size was .42 which is usually regarded a small to medium effect (Cohen, 1992). This emphasizes that relying on tests of significance when detecting effects can be problematic when sample sizes are small. Rather, it is necessary to consider the power of the test to detect actual effect if there is one in the population (Cohen, 1992).

Statistical power takes the effect size and sample size into consideration for estimating the test's probability of detecting an actual effect. It is also possible to estimate how many participants that would be needed to reach statistical power of .80, which is a convention proposed for general use (Cohen, 1992). For instance, power analysis showed that 108 people would be needed for 80% chance to detect an actual effect of early change in IUS-12 and late change in PTQ when $r = .18$. Power analysis were not conducted thoroughly in the present study, but given the small sample size it is likely that many detected effects lacked statistical power.

Type-I error means detecting an effect when there is no actual effect, and the risk of type-I error increases when sample sizes are small and when multiple analysis are conducted. This was the case in the present study, which conducted numerous correlation analysis including several variables. This means that although the level and change analysis gave significant relationships in many cases, it is not certain that they reflect actual relationships in the population.

The combination of low statistical power and high risk for type-I error means that the results must be interpreted with absolute caution.

Another limitation related to the small sample size is that the clinical sample could not represent all anxiety and mood disorders. A bigger sample would have allowed a more equal representation of different diagnoses, allowing more accurate conclusions about transdiagnostic effects. The present clinical sample consisted mainly of anxiety disorders which could have influenced the observed levels and changes of IU and RNT as well as symptom measures. A bigger sample could have cancelled out such an effect.

Furthermore, a limitation of the present study is that the researcher was not involved in the procedures at the clinic. This means that the researcher cannot be fully certain that all patients received the same instructions when asked to participate in the study, that the questions about the study or the questionnaires were answered correctly, how many sessions each participant attended, why some patients stopped responding to the self-report measures or other

factors that could have affected the results. On the other hand, this also means that the risk that the researcher should have affected the results in any way is minimal.

Doing psychotherapy research in natural clinical environments means compromising with internal validity. To be able to draw conclusions about treatment effect, study designs must include a relevant control variable, i.e. a wait-list control, a placebo condition or a control group receiving treatment as usual. Also, participants should represent the same population and be randomly assigned to either condition. This was not the case in the present study, meaning that indications of effect should not be regarded as representing actual effect. Essentially, the present study cannot confirm whether the changes in IU, RNT and symptom measures had anything to with the treatments or just represented spontaneous remission.

The degree to which the different treatment protocols targeted IU and RNT varied. The present study argued that the treatment protocols were more alike than different because they all target maintaining factors for negative affect. However, the exact degree to which the different treatment protocols targeted RNT and IU was not controlled for in the present study. Therefore, it cannot be concluded that the similarities were greater than their differences. It is possible that the differences in the treatment protocols could have had a greater impact on the results than their similarities. For example, the treatment protocol for GAD is especially focused on targeting IU, which could have contributed to the noted effect that a decrease in IU was correlated to decrease of anxiety, especially since 35% of the patients were treated for GAD. An interesting focus for future research could be to investigate whether changes in IU and RNT were different for patients receiving different treatment protocols. This could be one way to investigate the degree to which the treatment protocols target RNT and IU.

Also, because the length of therapy varied, not all therapies had reached the same stage after 8 weeks. This makes it difficult to make accurate comparisons between the treatment protocols. Patients who had completed therapy during the time of investigation had completed all treatment modules, whereas patients still under treatment probability had not. This means that the points of measurement possibly captured different stages of therapy in the clinical sample. For example, some patients may have started exposure interventions aimed at targeting RNT and IU, whereas others had not. A possible focus for future research in clinical setting is to investigate the change in IU, RNT and symptom measures at different points of measurement than the first three weeks of treatment, for example at the start, middle and towards the end of treatment even though not all therapies terminate within the data collection period. Such a change analysis could be more clinically relevant, as the chances to cover more stages of therapy increase.

The study design allowed very little control over the samples. It is certain that one group received CBT treatments during the data collection period, and that the other group did not. Other than that, there is no information about other factors that could have affected the way participants responded to the measures over time.

The reliance on observed change scores to estimate change has been subjected to controversy (Allison, 1990; Collins, 1996; Rogosa & Willet, 1985; Rogosa, 1988). More specifically, the change from early points of measurement to later are often subjected to regression to the mean, meaning that individuals who scored low at first points of measurement will tend to move up, and individuals with high initial scores will tend to move down (Allison, 1990). Hence, change scores may have been a rather imprecise estimate of change in IU, RNT and symptom measures in the clinical sample. When it comes to change during treatment, it is also possible that treatment factors could have affected the way in which participants responded. New insight into their symptoms gained during treatment could affect the way in

which the questions were interpreted, meaning that a clinical improvement not necessarily meant scoring lower.

Another limitation is that the data analysis could not accommodate the irregular fashion in which participants had responded to the self-report measures, leading to a big internal data loss. Other statistical methods, such as multilevel analysis, could have better accommodate this. Multilevel analysis could also be a good option because of its ability to assess change at different levels.

Suggestions for future research

The present study set out with the ambition to explore IU and RNT as possible mechanisms of change during disorder specific CBT in a natural clinical setting for patients with anxiety and mood disorders, and to investigate the relationship between IU and RNT. The study has met a number of challenges under its way. One of the biggest challenges has been to recruit and keep participants, which in turn has affected the possibility of getting statistical power in the data analysis. Another challenge has been the lack of a relevant control condition. The results from the present study must therefore be interpreted with caution. However, the experiences gained during the work with the present study can guide future research on IU and RNT as possible mechanisms of change in disorder-specific CBT.

Suggestions for future research on the subject is to include a considerably bigger clinical sample. To increase the possibility to draw conclusions on transdiagnostic effects, the sample size should be big enough to represent a balanced variety of anxiety and mood disorders. A bigger sample size could also increase the chances to detect actual effects in the population. Because of the challenges associated with recruiting and keeping patients in a natural clinical setting, the data collection period should be stretched over a long period of time, as a suggestion 1-2 years. Future studies could also consider limiting the inclusion criteria to a certain number of comorbid diagnosis. This would have the potential benefit of increased homogeneity regarding amount of clinical difficulties in the clinical sample.

Also, future studies should make efforts to analyse entire treatments, and to assess IU, RNT and symptoms multiple times during treatment. This would make comparisons between changes in the variables in different treatment protocols more accurate. Multiple assessments also enables the establishment of timelines, which means that it can be investigated whether changes in IU and RNT occur before changes in outcome measures, and whether change in IU predate change in RNT or vice versa, which is a way to assess their relationship more closely. In the case entire treatments cannot be assessed, future researchers could consider analysing points of measurement at the start, middle, and toward the end of treatments rather than assessing the first consecutive points of measurements, as was done in the present study. This has the potential benefit of capturing more stages of therapy, enabling more accurate comparisons between different treatments. Furthermore, the clinical implications of decrease in RNT, IU and symptom measures could be investigated. Also, future studies could include a pre-treatment measurement to be able to compare changes in RNT, IU and symptoms during treatment to changes in the corresponding variables before treatment. This could be one way to assess treatment effect if no control group is available.

A major gain for future studies on the subject would be to include a relevant control condition from the same populations as the clinical sample rather than a student sample. For instance, future studies could include a wait-list control, a placebo condition or a control group receiving another kind of therapy. This would allow investigation of treatment effect. An

interesting focus for future research would be to compare IU a RNT as mechanisms of change in disorder-specific CBT and in transdiagnostic CBT. Comparing to groups also opens up for more extensive data analysis. Specifically, it opens up for investigating whether IU and RNT mediate treatment effect, using multiple mediation analysis. Multiple mediation analysis could be conducted on data from multiple points of measurement, opening opportunities to investigate how changes in the mediators at different times during therapy affects the treatment effect.

In sum, the role of IU and RNT as possible transdiagnostic mechanisms of change in disorder-specific CBT treatments would be an interesting focus for future studies in natural clinical setting. If study designs can accommodate the challenges associated with psychotherapy research in a natural clinical setting, the results have the potential to increase the knowledge of how therapeutic change occur. This could be an important step toward developing effective treatment interventions to better accommodate comorbid and overlapping diagnoses in CBT.

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