

Relationships between Depressive Symptoms and Panic Disorder Symptoms during
Guided Internet-based Cognitive Behavior Therapy for Panic Disorder

Eirik P. Walderhaug^{a*}

Rolf Gjestad^b

Jens Egeland^{a,c}

Odd E. Havik^d

Tine Nordgreen^{d,e}

^a Division of Mental Health and Addiction, Vestfold Hospital, P.O. Box 2168 N-3103
Tønsberg, Norway.

^b Research department / Centre for Research and Education in Forensic Psychiatry,
Division of Mental Health, Haukeland University Hospital, P.O. Box 1400
N-5021 Bergen, Norway.

^c Department of Psychology, University of Oslo, P.O. Box 1094 Blindern, N-
0317 OSLO, Norway.

^d Department of Clinical Psychology, Faculty of Psychology, University of Bergen,
P.O. Box 7807, N-5020 Bergen Norway.

^e eMeistring, Division of Psychiatry, Haukeland University Hospital, Norway

* Corresponding author

E-mail addresses: eirik.paulsen.walderhaug@siv.no (E. P. Walderhaug),
rolf.gjestad@helse-bergen.no (R. Gjestad), jens.egeland@siv.no (J. Egeland),
Odd.Havik@uib.no (O. E. Havik), tine.nordgreen@uib.no (T. Nordgreen).

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Abstract

Aims:

The current study explore the relationship between the trajectories of primary panic disorder symptoms and secondary depressive symptoms during guided internet-delivered cognitive behaviour therapy for panic disorder.

Materials and methods:

The patients ($N=143$) were recruited from an ongoing effectiveness study in secondary mental health outpatient services in Norway. Weekly self-reported primary panic disorder symptoms and secondary depressive symptoms were analysed.

Results:

Primary panic disorder symptoms and secondary depressive symptoms improved significantly during the course of treatment, and at six months follow-up. Parallel process latent growth curve modelling showed that the trajectory of depressive symptoms and trajectory of panic disorder symptoms were significantly related. A supplementary analysis with cross-lagged panel modelling showed that (1) pre-treatment depressive symptoms predicted a positive effect of panic disorder symptoms early in treatment; (2) high early treatment panic disorder symptoms predicted low depressive symptoms at post-treatment.

Conclusions:

Guided ICBT for panic disorder is effective for both primary panic disorder symptoms and secondary depressive symptoms. Patients with high pre-treatment secondary depressive symptoms may constitute a vulnerable subgroup. A high level of panic disorder symptoms early in treatment seems beneficiary for depressive symptoms outcome. A time-dependent model may be necessary to describe the relationship between PAD symptoms and depressive symptoms during the course of treatment.

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Keywords: Guided ICBT, CBT, panic disorder, depression, comorbidity.

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1. Introduction

Cognitive behavioral therapy (CBT) is established as an effective treatment for panic disorder (PAD) (Cuijpers, Cristea, Karyotaki, Reijnders, & Huibers, 2016; Hofmann & Smits, 2008), and is the treatment of choice for PAD (National Institute for Health and Care Excellence, 2011). The treatment is designed to change specific panic-related cognitions and behaviors, thereby reducing the fear of panic related symptoms. A new mode of delivering CBT is guided internet-based CBT (guided ICBT). Guided ICBT is established as an empirically supported treatment for PAD, as defined by Chambless and Hollon (1998) (Andersson, 2009; Olthuis, Watt, Bailey, Hayden, & Stewart, 2016). A meta-analysis comparing the effects of guided ICBT and face-to-face delivered CBT found no significant difference in effects between these two modes of delivery in terms of reduction of symptoms or drop-out rates (Andersson, Cuijpers, Carlbring, Riper, & Hedman, 2014). Guided ICBT for PAD is also documented effective in regular clinical settings (Hedman et al., 2013; Nordgreen, Gjestad, Andersson, Carlbring, & Havik, 2017).

Depression is the most frequent comorbid disorder of PAD, besides other anxiety disorders (Kessler, Chiu, Demler, Merikangas, & Walters, 2005). Anxiety disorders often precede depression, suggesting that major depression often is secondary to PAD (Wittchen, Beesdo, Bittner, & Goodwin, 2003; Wittchen, Kessler, Pfister, Höfler, & Lieb, 2000). Several studies have found that CBT for PAD also lead improvement in secondary depressive symptoms (Allen et al., 2010; Emmrich et al., 2012; Tsao, Mystkowski, Zucker, & Craske, 2002). Several studies have also shown that guided ICBT for PAD lead to improvement in secondary depressive symptoms (Hedman et al., 2013; Nordgreen et al., 2017). However, the relationship between primary PAD and secondary depressive symptoms during treatment is not well understood.

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A decrease in depressive symptoms as a result of PAD focused treatment could have several explanations. One explanation is: (1) the treatment leads to a reduction in a common feature in both depression and anxiety disorder, sometimes called “negative affect syndrome” (Barlow, Allen, & Choate, 2004; Brown, Chorpita, & Barlow, 1998; Clark & Watson, 1991); (2) reduction in anxiety symptoms lead to behavior activation, which is a hypothesized change factor in psychological treatment for depression (Dimidjian et al., 2006; Richards et al., 2016); (3) the reduction in both PAD symptoms and depressive symptoms are due to common change factors in psychological treatment, such as the therapeutic relationship and hope (Lambert, 1992; Wampold & Imel, 2015).

Several studies have found a significant relationship between the trajectory of anxiety symptoms and the trajectory of depressive symptoms during treatment (Aderka, Gillihan, McLean, & Foa, 2013; Moscovitch, Hofmann, Suvak, & In-Albon, 2005; Zandberg et al., 2015). Some of these studies have demonstrated a significant relationship between the trajectory of anxiety related symptoms at one time point and the trajectory of depressive symptoms at a later time point (Aderka et al., 2013; Zandberg et al., 2015), suggesting a causal relationship between these symptoms. However, there is a lack of knowledge about this relationship in PAD.

The present study investigated the trajectories of primary PAD symptoms and secondary depression symptoms during ICBT for PAD. Our hypotheses were: (1) ICBT for PAD is effective in reducing depressive symptoms; and (2) the relationship between the trajectory of PAD symptoms and the trajectory of depressive symptoms is significant.

2. Materials and methods

2.1. Clinical treatment setting

The participants ($N = 143$) were treated with guided ICBT (Carlbring, Westling, Ljungstrand, Ekselius, & Andersson, 2001; Nordgreen et al., 2010). The same treatment was

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provided in two treatment sites in Norway, one in the Bergen area ($n = 134$), and one in the Vestfold area ($n = 9$).

2.2. Design

The design was an open pre-post, 6 month follow-up effectiveness study. The treatment was done as a part of routine care from December 2013 to May 2016. It used repeated measurements of PAD symptoms and depressive symptoms at each of 9 treatment modules, and at six months follow-up. The study was approved by the Regional Ethics Committee for research with human subjects (reference number 2012/2211).

2.3. Participants

The participants were referred to secondary mental health services from their general practitioner. They were evaluated and found eligible for services in the Norwegian specialist mental health system. To be eligible for treatment for an anxiety disorder the condition must be considered severe and with marked limitation of daily functioning (Norwegian Directorate of Health, 2008). Those found eligible for services were given a face-to-face mental health assessment interview by a mental health professional, including the Mini-international neuropsychiatric interview (MINI, Sheehan et al., 1998). Inclusion criteria were: (1) panic disorder diagnosis criteria satisfied according to the MINI, (2) 18 years of age or above, (3) stable dose of antidepressants or other types of medication, (4) ability to read and understand the written self-help material in Norwegian. Exclusion criteria were (a) active psychosis, (b) severe major depression, (c) high suicide risk, (d) active substance abuse or (e) active use of sedatives. If the patient declined the invitation, they were offered treatment as usual, and not included in the study. Participation in the study was based on informed and signed consent.

The treatment program was still continuing as we extracted the data for our analysis, and we did not distinguish between the participants who had dropped out of treatment, those who were still in treatment and those who had completed treatment. All participants who

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completed the measures of panic symptoms and depressive symptoms at one or more occasions were included.

2.4. Procedure

2.4.1. Treatment

All participants were given guided ICBT for PAD. The treatment program was previously shown to be more efficacious than a waitlist condition in a randomized controlled trial (Carlbring et al., 2001). It was also shown to be equally efficacious as face-to-face CBT for PAD (Carlbring et al., 2005). It remained effective when transported to a Norwegian context (Nordgreen et al., 2017; Nordgreen et al., 2010). The treatment program was manualized, and consisted of nine weekly modules, which were completed in a period of maximum 14 weeks. Each module consisted of about 15 pages of written text for the participants to read; a set of assignments, consisting of questions regarding the text, or exposure tasks. The first three modules contain an introduction to self-help, cognitive behavioral therapy, and psychoeducation about PAD and agoraphobia. The principle model was Clark's (1986) model for PAD (the panic circle). Module 4-7 contained cognitive restructuring and behavioral experiments regarding bodily reactions and agoraphobic avoidance. The last two modules (8-9) contained summary and relapse prevention. The treatment did not have explicit focus on depressive symptoms and did not target depressive cognitions.

2.4.2. Therapist guidance

Each week, the participants were given feedback from a therapist on their assignments and progression. The therapists were licensed clinical psychologists, medical doctors, nurses or social workers. All the therapists had received adequate training in delivering the treatment. The participant's advancement to the next module was contingent on the therapist evaluating the work in the module as satisfactory, and not on the time used.

2.5. Assessments and Measures

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2.5.1. Diagnostic assessment

The participants were assessed for presence of panic disorder with the MINI-International Neuropsychiatric Interview (MINI, Sheehan et al., 1998), and diagnosed according to the ICD-10 diagnostic manual (World Health Organization, 1992). The English version of the MINI has excellent inter-rater and test-retest-reliabilities, and moderate concurrent validity (Lecrubier et al., 1997; Sheehan et al., 1998; Sheehan et al., 1997). The Norwegian version has shown excellent psychometric properties for the PAD module (Mordal, Gundersen, & Bramness, 2010).

2.5.2. Primary PAD symptoms

PAD symptoms were measured with the self-report questionnaire Bodily Sensations Questionnaire (BSQ, Chambless, Caputo, Bright, & Gallagher, 1984). BSQ comprises 16 items on a scale from 1 (not frightened or worried by this sensation) to 5 (extremely frightened by this sensation), regarding bodily sensations commonly experienced during autonomic nervous system arousal. The measure was previously found to be sensitive to change during treatment (Chambless et al., 1984). The internal consistency of the pre-treatment BSQ scores in the present study was good ($\alpha = .85$). The patients were asked to complete the BSQ at pre-treatment, and at treatment modules 2 through 9, and at 6-months follow-up assessment.

2.5.3. Secondary depressive symptoms

Depressive symptoms were measured with the Montgomery Åsberg Depression Rating Scale, Self-rating version (MADRS-S; Montgomery, & Åsberg, 1979). MADRS-S comprises 9 items rated on a scale from 0 (no evidence of symptom) to 6 (pervasive evidence) assessing depressive symptoms. The measure has previously been found to be sensitive to change (Montgomery & Åsberg, 1979). The internal consistency of the pre-treatment MADRS-S

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scores in the present study was good ($\alpha = .87$). The patients were asked to complete the MADRS-S at pre-treatment, and at treatment modules 1-9, and at 6-months follow-up.

2.6. Statistical analyses

Data preparation and calculation of descriptive statistics were conducted using IBM SPSS version 21 (Spss, 2012). All structural equation modeling was conducted using Mplus, version 7.4 (Muthén & Muthén, 1998-2015).

Latent growth curve modeling was used to model the level and change of the PAD symptoms and depressive symptoms trajectories separately (Wang & Wang, 2012). A latent growth model with freely estimated time factors (Muthén & Muthén, 1998-2015, example 6.8) provided satisfactory fit. In this model, the loading of the score from the pre-treatment measurement on the change factor was fixed to 0, the loading on the last measurement (at module 9) on the change factor was fixed to 1, and the loadings of the other measurement points on the slope factor were freely estimated. To achieve satisfactory model fit, the models were re-specified with freely estimated residual correlations in the measurement of each construct at different measurement points, if this led to a significantly better model fit.

Parallel process latent growth curve modeling (Meredith & Tisak, 1990) was used to model the relationship between the trajectories of PAD symptoms and the trajectory of depressive symptoms (Muthén & Muthén, 1998-2015; Wang & Wang, 2012). The starting point for this model was the two separate latent growth models of PAD symptoms and depressive symptoms, respectively. To achieve satisfactory model fit, the model was re-specified with freely estimated correlations between residuals of PAD symptoms and depressive symptoms measured at the same time point, if this led to a significantly improved model fit.

A cross-lagged panel model was used as an exploratory analysis, to investigate the direction and temporal relationship between primary PAD symptoms and secondary

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depressive symptoms. This model type is commonly used to investigate possible causality, interpretations must be done with caution (T. D. Little, 2013). To reduce model complexity, four of the ten measurement points were used for the analysis model (pre-treatment, and module 3, 6 and 9). First-, second- and third order autoregressive and cross-lagged relations were modeled. To achieve satisfactory model fit, the model was re-specified with freely estimated correlations between residuals of PAD symptoms and depressive symptoms measured at the same time point, if this led to a significantly improved model fit.

Model fit was evaluated using the root mean square error of approximation (RMSEA; Steiger & Lind, 1980) the standardized root mean residual (SRMR; Muthén & Muthén, 1998-2015), the comparative fit index (CFI; Bentler, 1990), and the non-normed fit index (NNFI; Bentler & Bonett, 1980). A RMSEA value less than .05 is regarded as close fit, less than .08 as acceptable, and less than .10 as mediocre fit (Browne & Cudeck, 1993; Steiger, 2007). A SRMR value less than .08 is regarded as acceptable (Hu & Bentler, 1999). With both the CFI and the NNFI, a value larger than .90 is regarded acceptable fit (Hu & Bentler, 1999) and .95 as a good fit (Wickrama, Lee, O'Neal, & Lorenz, 2016). When re-specifying the model, the improvement was considered significant if the χ^2 statistic was decreased by 3.84, corresponding to significance at $p=.05$ level, and if the modification resulted in an improvement in model fit (*i.e.* a reduction in RMSEA and SRMR, and an increase in CFI and NFI values).

Handling of missing data was done by Full Information Maximum Likelihood Estimation (FIML), a method which has been shown to perform better than alternative methods of handling missing data (Enders & Bandalos, 2001). FIML assumes that data are missing at random (MAR) (McKnight, McKnight, Sidani, & Figueredo, 2007; Schafer & Graham, 2002). This assumption was tested using Little's test for MCAR (R. J. A. Little, 1988), which indicated that the missing data were MCAR, and that the assumption therefore held.

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3. Results

3.1. Pre-treatment characteristics

Mean age of the participants was 34.9 years ($SD = 11.5$, Range 18.7 – 68.3, $N = 143$). There were 58.7 % women ($N = 143$). Mean pre-treatment BSQ was 2.74 ($SD = 0.68$, $N = 142$), and mean pre-treatment MADRS-S was 16.9 ($SD = 8.7$, $N = 143$). The participants from the two sites did not differ significantly from each other on age, gender, or on any pre-treatment, final module or six months follow-up symptom measure ($P > .05$ on all comparisons).

3.2. Depressive symptoms were reduced during and after treatment

Insert Table 1 about here

Regarding hypothesis 1, Table 1 shows means and standard deviations for depressive symptoms during the treatment period and at follow up assessment. Depressive symptoms were reduced during the treatment period, and there were large pre-post within-subjects effects (Cohen's $d = 0.86$). The improvement was retained at follow-up (Cohen's $d = 0.90$).

Insert Figure 1 about here

Figure 1 shows the model generated growth plots for PAD symptoms and depressive symptoms. The model provided a satisfactory model fit, for both the PAD symptoms and depressive symptoms trajectories. (Model fit for PAD symptoms: $\chi^2(31) = 41.70$, $p = .095$; RMSEA = .049, 90% CI: .000, .085, CFI = .981, NNFI = .978, SRMR = .129; Model fit for depressive symptoms: $\chi^2(41) = 46.70$, $p < .250$; RMSEA = .031, 90% CI: .000, .068, CFI = .993, NNFI = .993, SRMR = .044).

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The results from the modelling of the depressive symptoms indicated a statistically significant reduction from pre-treatment to post-treatment (mean slope factor = $-5.17 \pm .85$, $p < .001$). The results from the modelling of the PAD symptoms also showed a significant reduction from pre-treatment to post-treatment (mean slope factor = -0.89 ± 0.07 , $p < .001$).

Insert Figure 2 about here

3.3. Trajectories of PAD symptoms and depressive symptoms were related

Regarding hypothesis 2, the results of the parallel process growth curve model for the relationship between the trajectories of PAD symptoms and depressive symptoms are showed in *Figure 2*. This model provided satisfactory model fit ($\chi^2(153) = 240.23$, $p < .001$; RMSEA = .063; 90% CI: .047, .078; CFI = .951; NNFI = .946; SRMR = .091).

There was a significant correlation between change in PAD symptoms and change in depressive symptoms ($P < .001$). The correlation coefficient was .50, indicating a large effect (Cohen, 1988).

Insert Figure 3 about here

3.4. Exploratory analysis

To investigate causality, we explored the relationship between the variables further, based on our results from hypotheses 1 and 2. The results from the cross-lagged panel model are shown in *Figure 3*. This resulted in a saturated model, and therefore a perfect fit.

3.4.1. High depressive symptoms at pre-treatment predicted an increase in PAD symptoms early in treatment

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The results showed that pre-treatment depression symptom level (D_0) positively predicted the level of early treatment PAD symptoms (at P_3). This indicates that a high pre-treatment depressive symptoms predicted high PAD symptoms at module 3. Pre-treatment depressive symptoms negatively predicted mid-treatment PAD symptoms (P_6), meaning that high pre-treatment depressive symptoms predicted low PAD-symptoms at module 6. These two effects are equal in size, and seem to cancel each other out, making this a temporary effect.

3.4.2. High PAD symptoms early in treatment predicted low depressive symptoms at post-treatment

High PAD symptoms at module 3 predicted low post-treatment depressive symptoms. All other cross-lagged relationships were non-significant.

4. Discussion

The aim of the study was to investigate the relationships between primary PAD and secondary depression symptoms during ICBT for PAD. Our hypotheses were confirmed: (a) guided ICBT for PAD was effective in reducing primary PAD and secondary depressive symptoms. (b) The correlation between the trajectory of primary PAD and the trajectory of secondary depressive symptoms during treatment was significant. In addition did our exploratory analysis show clinically interesting and significant relationships between PAD symptoms and depressive symptoms during treatment. Below follows a discussion of the results.

Both the pre-post treatment effect size and pre-treatment follow-up effect size for depressive symptoms were large (Cohen, 1988). This result shows that guided ICBT for PAD lead to significant reduction in depressive symptoms. Depressive symptoms reduced significantly as a result of treatment with no specific focus on depressive symptoms or cognition. This result was as expected, given that other studies have shown reduction in

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depressive symptoms after both face-to face CBT and guided ICBT for PAD (Allen et al., 2010; Emmrich et al., 2012; Hedman et al., 2013; Nordgreen et al., 2017; Tsao et al., 2002).

The correlation between the trajectory of depressive symptoms and the trajectory of PAD symptoms was significant. This means that the trajectories of PAD symptoms and depressive symptoms follow each other in time during the course of treatment. The participants with a relatively large improvement in PAD symptoms tend to have relatively large improvement in depressive symptoms, while the patients who have relatively small improvements in PAD symptoms tend to have small improvements in depressive symptoms. This effect was large. To our knowledge this is the first study showing the relationship between PAD-specific CBT and depressive comorbid symptoms, for any mode of CBT. It is also the first study showing this relationship in the context of guided ICBT for any anxiety disorder. The result is in line with other studies showing this relationship for social phobia (Moscovitch et al., 2005), post-traumatic stress disorder (Aderka et al., 2013) and obsessive-compulsive disorder (Zandberg et al., 2015).

Regarding clinical implications, our results indicate that ICBT for PAD lead to a reduction in secondary depressive symptoms. This indicates that the treatment is effective for patients with PAD with primary PAD symptoms and secondary depressive symptoms. The finding that participants with high pre-treatment depressive symptoms predicted an elevation of PAD symptoms early in treatment has clinical implications. This may be a vulnerable group where the therapists should install hope in the participants, and motivate them to continue the treatment in spite of this temporary increase of symptoms. Another finding with a clinical implication was that high PAD symptoms early in treatment predicted low depressive symptoms at post-treatment. Consequently, the PAD symptom elevation early in treatment was associated with a reduction of depressive symptoms at post-treatment.

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As of theoretical implications from our results, no clear one-way causal relationship between PAD symptoms and depressive symptoms were found. Rather, our exploratory analysis revealed relationships both ways: one way from pre-treatment depressive symptoms to early and middle treatment PAD-symptoms, the other from early treatment PAD symptoms to post-treatment depressive symptoms (see Figure 3). This suggests causal relationships both ways between PAD symptoms and depressive symptoms, which changes in nature as the treatment progresses.

4.1. Limitations

The main limitation of the current study was the lack of a control group. We can therefore not be certain that improvement in PAD symptoms and depressive symptoms in the present study was due to the treatment. Secondly, the models of fit of these data were good, but not excellent. The findings therefore need to be replicated with a larger sample size.

4.2. Strengths

The present study had several strengths. First, the study used repeated measurements with high frequency, allowing for the non-linear shape of the trajectories to be described in the model, thereby improving the validity of the results, and allowing for the investigation of the changing relationship between the factors during the course of treatment. Secondly, it used a naturalistic design, with wide inclusion criteria, with GP-referred participants, representing a more chronic population than found in self-referred samples. Together, this leads to a strong ecological validity. Finally, the study had a relatively large sample size, which increased the generalizability of the results.

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Declaration of interest statement

The authors declare that there are no conflicts of interest.

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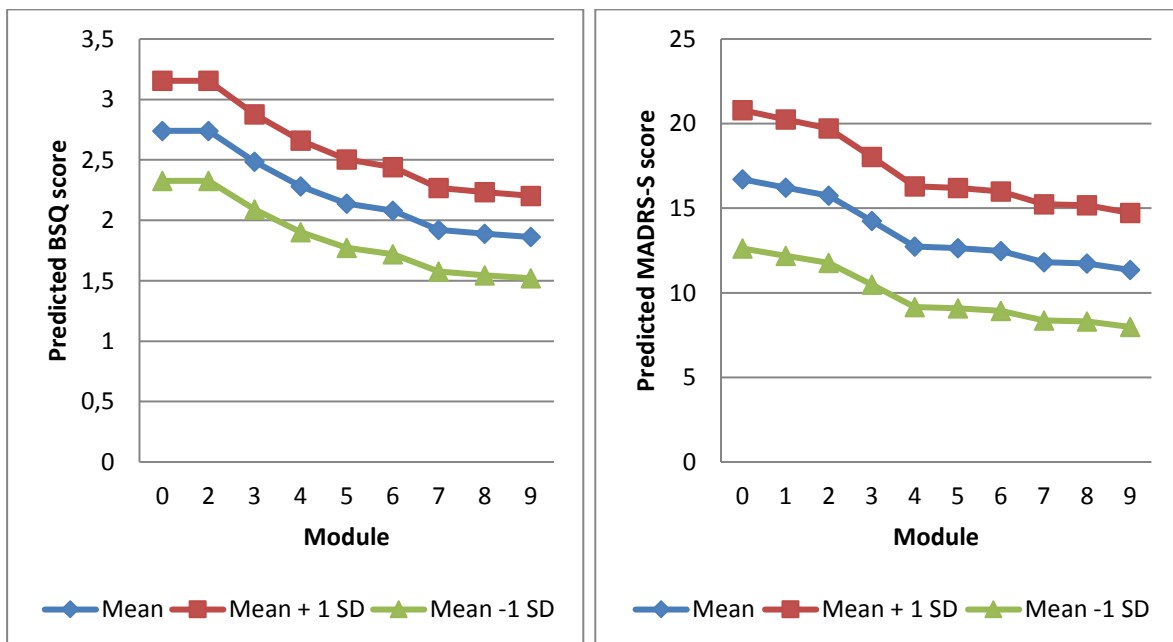
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Table 1. Descriptive statistics (means, standard deviations) for depressive symptoms.

Module	N	MADRS-S	
		M	SD
0	143	16.9	8.66
1	134	16.0	8.51
2	121	16.2	9.40
3	110	15.5	9.39
4	91	13.1	8.88
5	83	12.7	9.38
6	65	11.5	8.66
7	54	10.4	8.24
8	48	10.0	9.60
9	44	9.45	8.98
FU-6	25	9.08	7.58

Note: MADRS-S = Montgomery Åsberg Depression Rating Scale, Self-Report version (MADRS-S). FU-6 = 6 months follow-up assessment. Module 0 means at pre-treatment assessment.



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Figure 1. Model-generated growth plots for PAD symptoms and depressive symptoms. Plots show the model-estimated means and means ± 1 SD at pre-treatment (shown as module 0) and at all treatment modules.

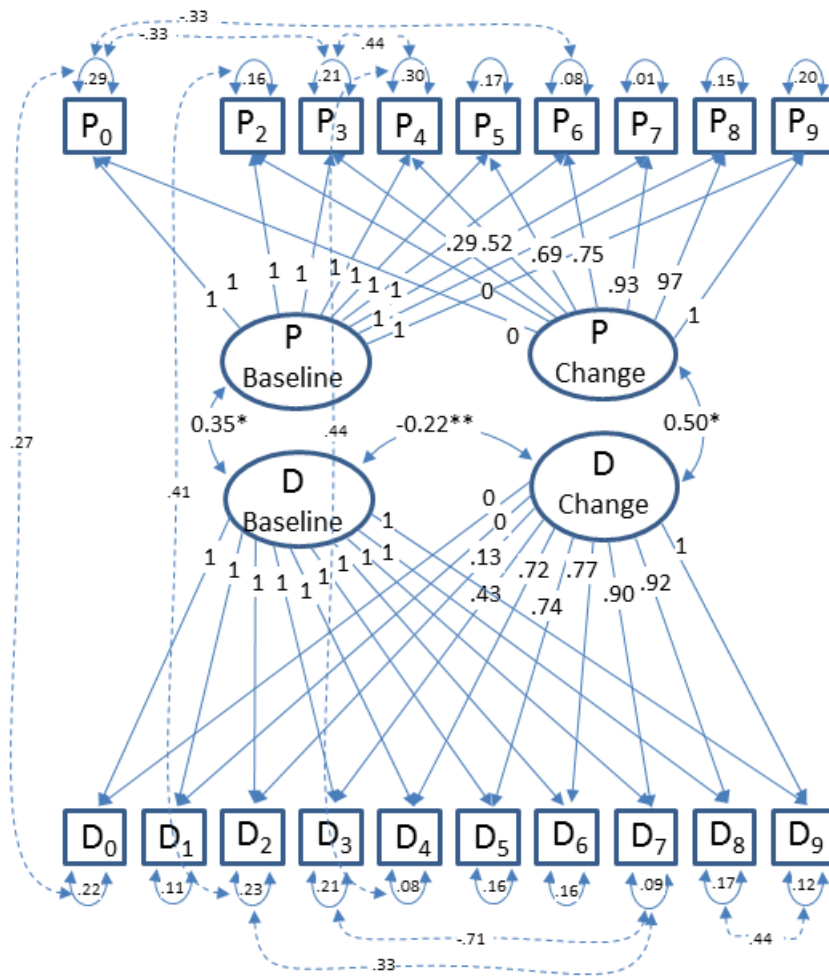


Figure 2. Standardized results from the parallel process latent growth curve model of panic symptoms and depressive symptoms. Only significant relationships are shown. Note: P = panic disorder symptoms, measured with the Bodily Sensations Questionnaire (BSQ), D = depressive symptoms, measured by the Montgomery Åsberg Depression Rating Scale, Self-Report version (MADRS-S), * significant at $P < .001$, ** significant at $P < .05$. Correlations between residuals are shown with dotted lines for clarity.

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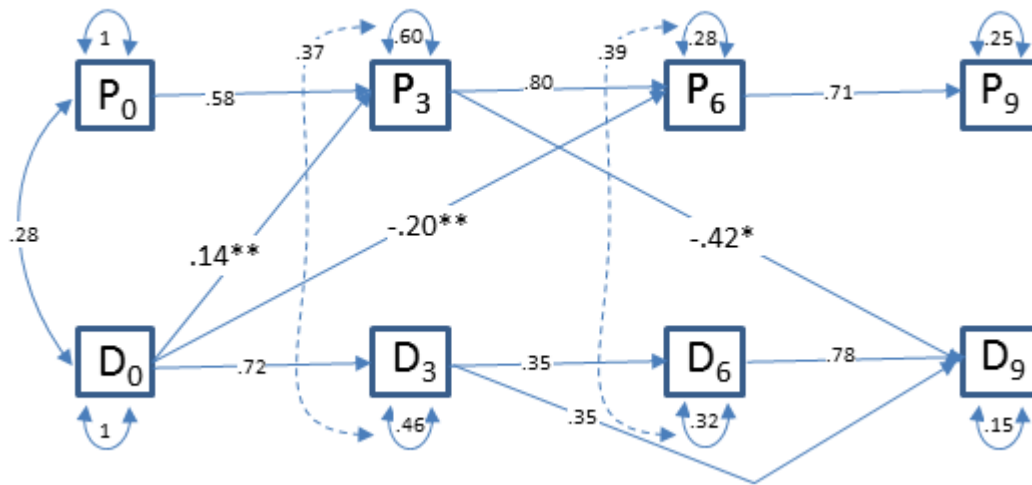


Figure 3. Standardized results from the autoregressive cross-legged panel model of panic disorder symptoms and depressive symptoms.

Note: P = panic disorder symptoms, measured by the Bodily Sensations Questionnaire (BSQ), D = depressive symptoms measured by the Montgomery Åsberg Depression Rating Scale, Self-Report version (MADRS-S), * significant at $P < 0.01$, ** significant at $P < 0.05$. Correlations between residuals are shown with dotted lines for clarity.