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Which Panic Disorder Patients Benefit from Which Treatment: Cognitive Therapy or Antidepressants?

Elise Dusseldorp[a] Philip Spinhoven[b] Abraham Bakker[c] Richard van Dyck[c] Anton J.L.M. van Balkom[c]

[a]Data Theory Group, Department of Education, [b]Section of Clinical and Health Psychology and Department of Psychiatry, Leiden University, Leiden, and [c]Department of Psychiatry and Institute for Research in Extramural Medicine, VU-University Medical Centre and GGZ Buitenamstel, Amsterdam, The Netherlands

Key Words

Panic disorder · Cognitive therapy · Antidepressants · Locus of control · Moderator · Differential effectiveness · Treatment effectiveness · Aptitude-treatment interaction · Regression trunk approach

Abstract

Background: Beliefs about the controllability of a disorder may be relevant in the causation, maintenance and treatment of disorders. We investigated whether congruence between patients' beliefs about controllability of a panic disorder and the type of treatment provided predicted outcome. ***Methods:*** The differential effectiveness of cognitive therapy and antidepressant treatment (paroxetine or clomipramine) was investigated in a sample of 129 panic disorder patients in a 12-week, pretest posttest placebo-controlled study. Panic frequency, agoraphobic avoidance, anxiety, depression, and disability were measured with various validated interviewer and self-report measures. Beliefs about controllability were measured with the Multidimensional Anxiety Locus of Control Scale measuring an internal, chance, therapist and medication locus of control. In order to analyze aptitude-treatment interactions a new strategy called the Regression Trunk Approach was used in addition to classical hierarchical multiple regression analysis. ***Results:*** Using the Regression Trunk Approach we found that locus of control orientation (LOC) predicted the differential effectiveness of cognitive therapy. Those patients with a medium internal LOC who received cognitive therapy performed significantly better than all patients who received a placebo pill on 8 of the 10 outcome variables. We did not find a differential LOC effect for antidepressant treatment. No evidence for aptitude-treatment interactions using hierarchical multiple regression analysis was found. ***Conclusions:*** Moderately strong beliefs about self-control of panic disorder congruent with the cognitive intervention provided seem to moderate treatment effectiveness. Future studies must be more attentive to the nonlinear effects of patient characteristics on the outcome of different types of treatments.

Introduction

The general question of 'which person benefits from which type of treatment?' is the core question of aptitude-treatment interaction (ATI) research. Cronbach [1] may be considered as the founder of the ATI concept. ATI can be defined as the degree to which results of two or more treatments differ for persons who also differ on one or more aptitudes (i.e. person characteristics [2]). In ATI

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Elise Dusseldorp, PhD
Faculty of Social and Behavioural Sciences, Data Theory Group
Department of Education, Leiden University
PO Box 9555, NL–2300 Leiden RB (The Netherlands)
Tel. +31 71 527 3620, Fax +31 71 527 3865, E-Mail dusseldorp@fsw.leidenuniv.nl

analysis, individual differences are not considered as 'error variance', as in analysis of variance, but as important sources of possible differential effectiveness of treatments [3].

The present study focuses on predictors of the differential effectiveness of two treatments for panic disorder: pharmacological therapy with antidepressants (AD) and cognitive therapy (CT). Although many researchers underlined the importance of systematic selection of persons to psychological treatments [4], relatively few experimental clinical studies were found that report significant ATI effects [5]. We found no studies demonstrating ATI effects in panic disorder patients. Several meta-analyses, however, demonstrated the overall effectiveness of both panic disorder treatments (AD or CT) [6, 7]. The mean overall effect size was highest for cognitive-behavioral treatments relative to pharmacological and combination treatments [6]. In contrast to these results, Bakker et al. [8] found in their single study that AD was superior to pill-placebo on all outcome measures, whereas CT was only superior to pill-placebo on 2 of the 10 outcome measures. These results challenged us to investigate in this study, by means of secondary analyses, whether CT had been successful only for a subgroup of patients, and also whether AD treatment had been more successful for a subgroup of patients.

Several studies noticed the importance of the concept of locus of control (LOC) for the effectiveness of psychological treatments [9], and for the prediction of anxiety [9, 10]. Barlow concluded that in general a sense of relative uncontrollability functions as a mediator between environmental events and anxiety or depression in early childhood, and as a moderator in late childhood and adulthood. In addition, it has been emphasized that enhancing mastery and confidence in self-control are important ingredients in anxiety management treatments [11]. LOC evolved from a general concept indicating a person's expectation about how reinforcement is controlled [12] to more specific concepts, for example, a patient's beliefs about the controllability of an anxiety disorder (the Multidimensional Anxiety Locus of Control scale [13]). Liberman [14] investigated the influence of LOC in a small sample of psychiatric outpatients who were referred for psychotherapy. He found that patients with an internal LOC improved more in a self-attributed success condition, whereas patients with an external LOC improved more in an externally attributed success condition (a placebo pill). Reich and Zautra [15] recruited older adults who had suffered from either a physical disability or a conjugal bereavement. These adults were individually matched with adults who had experienced neither major event. They showed that the mental health of adults with a high internal LOC improved most with a control-enhancement intervention, and the mental health of those with a low internal LOC improved most with a placebo social contact group. The authors concluded that the control-enhancement intervention was congruent with the mastery beliefs of the high internals.

The relatively low number of studies reporting significant ATI effects might be attributed partly to the method of data analysis used. In most studies, a classical analysis approach to ATI was applied. This approach is based on hierarchical multiple regression analysis. An ATI effect is estimated by computing a cross-product of a dichotomous treatment variable and a continuous aptitude variable. The model can be extended to assess multiple ATIs by adding more cross-products. In two studies reviewed above [14, 15], an analysis of variance approach was applied. In this approach, the continuous aptitude variable is categorized before the analysis, mostly into two categories (at the median). Cronbach and Snow [16] strongly advised against this dichotomization of a continuous aptitude variable because of its loss of statistical power. Recently, an alternative approach has been proposed, called the Regression Trunk Approach (RTA) [17]. RTA assesses whether threshold interactions occur, that is, whether the effect of a predictor variable on a response is different for those persons who score above and those who score below a certain threshold value (i.e. cut-off point) on another predictor variable. With respect to ATI, the method can identify the change point in an aptitude, above which (or below which) persons appear to be more responsive to a specific therapy. As Snow [2, p. 215] noted: 'For each type of person and treatment situation there is likely to be a threshold or zone within which optimal effect is achieved and outside of which it is not.'

On the basis of the above-mentioned studies and our own clinical experience, two hypotheses were formulated. Firstly, we hypothesized that patients with a lower internal LOC will benefit less from CT. These patients are convinced that they cannot control their panic attacks themselves. For example, they think that they cannot decrease their anxiety level by altering their negative automatic misinterpretations of benign bodily sensations (one of the goals of cognitive therapy). Because cognitive therapy is directed at enhancing the self-management of the patient, it is likely that this type of treatment will be less effective in patients continuing to believe that they cannot influence their illness with their own behavior. Secondly, we hypothesized that patients with a higher

medication LOC will benefit more from AD. These patients believe that especially medication influences their illness. More specifically, they have a stronger belief in the controllability of their panic disorder through the use of an active drug. Because the AD intervention is congruent with this belief, we expected that AD would be more effective for patients with a higher medication LOC compared to patients with a lower medication LOC.

Because we had no rationale about possible threshold values on the LOC subscales, we preferred the regression trunk approach as analysis method. This method finds one or more optimal thresholds on a predictor variable. Internal LOC and medication LOC are two of the four subscales measured by the Multidimensional Anxiety Locus of Control Scale [13]. We were also interested in the possible influence of the other two subscales (therapist LOC and chance LOC). Therefore, the primary objective of this study was to explore whether and how pretest locus of control (indicated by four subscales) moderated the effectiveness of treatment, either cognitive therapy or antidepressants. The pill-placebo condition served as control condition. The secondary objective was to confirm the exploratory results found for one outcome variable on the remaining nine outcome variables.

Method

Participants and Design

In a 12-week, pretest posttest placebo-controlled study, 131 patients with panic disorder were randomly assigned to four conditions: paroxetine (n = 32), clomipramine (n = 32), cognitive therapy (n = 35), or pill-placebo (n = 32) (see for a detailed description of the treatments and experimental design: [8]). In addition, 31 patients who had refused randomized treatment received cognitive therapy (CT) by preference [18]. During a run-in period before the start of the study, all patients received placebo treatment. The pretest measurement was at the end of this run-in period and the posttest measurement was at the end of the 12 weeks of active treatment.

Drop-out rates from pretest to posttest were 12.5% for the paroxetine group, 9.4% for the clomipramine group, 25.7% for the CT by allocation group, 22.6% in the CT by preference group, and 6.3% in the pill-placebo group. Those who dropped out did not differ significantly from those who remained in the study on demographic variables and on each of the four locus of control scales. At the posttest, no significant differences were found on seven of the ten outcome variables between the two groups of patients who completed treatment with antidepressants, either paroxetine or clomipramine [8]. In addition, no significant differences were found on all outcome variables between the two groups of patients who completed treatment with CT, either by chance allocation or by their own preference [18]. Because of these findings we merged the patients who completed treatment with antidepressants into one group (AD; n = 57) and patients who completed treatment with CT into another group (n = 50). We also included the patients who completed the pill-placebo condition (PL; n = 30). The mean age of these 137 patients was 34.8 years (range 18–55), and 68% (n = 93) were female. The duration of the panic disorder varied between 0 and 28 years (mean is 7 years). The severity of the panic (according to DSM-III-R) was moderate for 38% and severe for 62% of the patients. The three treatment groups did not differ significantly with regard to these demographic and medical variables.

Measures

At the pretest, patients reported the duration of their panic disorder, and they were asked to complete the Multidimensional Anxiety Locus of Control Scale (MALC), derived from the Multidimensional Health Locus of Control Scale [19]. The MALC pertains to the measurement of locus of control in panic disorder patients. The items of the MALC reflect patients' generalized expectancies about which type of factors control their panic attacks (i.e., internal, chance, medication, and therapist factors). The four subscales of the MALC are validated by a principal components analysis (see [13]) and the reliability coefficients (Cronbach's α) are 0.77 (internal LOC; 6 items), 0.75 (chance LOC; 6 items), 0.86 (medication LOC; 3 items), and 0.67 (therapist LOC; 3 items). Examples of items are 'When I get a panic attack, I am to blame' (internal LOC), 'Luck plays a big part in determining how soon I will recover from a panic attack' (chance LOC), 'If a panic attack subsides, I feel it's mainly due to medication' (medication LOC), and 'Having regular contact with a therapist is the best way for me to avoid panic attacks' (therapist LOC). The response scale of each item ranged from 1 ('totally agree') to 6 ('totally disagree'). Also the subscales ranged from 1 to 6, and were recoded in such a way that 6 indicated a high control orientation. The correlations between the four scales varied from –0.41 (between internal and chance LOC) to 0.24 (between medication and therapist LOC). No significant correlation was found between each of these LOC subscales and age, gender, and duration of panic disorder of the participants, except for medication LOC and duration of panic disorder ($r = 0.20$, $p = 0.02$).

We used the following validated measurement instruments (see for references [8]), administered at pre- and posttest: the Hamilton Rating Scale for Anxiety (HAMA), the Montgomery-Asberg Depression Rating Scale, the Clinical Global Impression-Severity of Illness score, the Marks-Sheehan Phobia Scale (including both an anxiety and an agoraphobia scale), the Patient Global Evaluation (PGE), and the Sheehan Disability Scale (SDS). Furthermore, the patients gave an Overall Phobia Score and an Anticipatory Anxiety Score (both range from 0 to 10). During the run-in period, patients recorded their panic attacks in diaries on a daily basis. The pretest panic frequency was the average panic frequency over the run-in period. The posttest panic frequency was the average frequency of weeks 10–12.

Of the ten outcome variables, the HAMA was chosen to perform a RTA analysis. Cognitive behavioral methods are found to be superior in reducing anxiety levels, frequently measured with the HAMA, compared to control conditions (d = 1.3) [7]. In the study of Bakker et al. [8], however, no main effect for CT was found on the HAMA. Given this result, we were interested whether CT had led to a decreased anxiety level in a subgroup of patients.

Statistical Analysis

The Regression Trunk Approach (RTA) to ATI. RTA combines multiple linear regression with regression trees. Multiple regression analysis is used to estimate both the main effects of predictor variables (i.e. independent variables) and the threshold interaction effects between predictor variables [17]. These threshold interaction effects are the ATI effects. In this study, we used posttest HAMA as outcome variable (i.e., dependent variable), and the following variables, all measured at the pretest, as predictors: HAMA, duration of panic disorder, agoraphobia, two dummy variables indicating type of treatment condition (CTdum: CT vs. placebo; ADdum: antidepressants vs. placebo), and the four LOC variables. It is essential for the assessment of ATI effects that all the predictors are measured at the pretest [16]. Duration of panic disorder and agoraphobia were included, because they represented two important predictors (i.e. their main effects were significant for several outcome variables; see table 2). The four LOC variables and the treatment variable were included as predictors to test our hypotheses regarding ATI effects.

In RTA, the ATI effects are represented by dummy variables. Each dummy variable can be seen as an interaction effect between the treatment variable and one or more other predictors. For example, a value 1 on a dummy variable may indicate those patients who score higher than 3.10 on internal LOC and who received CT. To construct such a dummy variable, a regression tree is estimated. We will first explain how regression trees work in general, before describing the details of RTA.

Regression trees are part of a broader method, called CART, which stands for Classification And Regression Trees [20]. A regression tree can be seen as a stepwise one-way analysis of variance. The tree analysis starts with the total sample in the so-called root node. The mean of the outcome variable is computed, and the corresponding total sum of squares[1]. The total group is divided into two subgroups, the left and right child nodes on the basis of a split point on a predictor variable. The mean of the outcome variable in the left and right child node is computed, and the corresponding total sum of squares. The tree algorithm computes for each possible split point on each predictor the resulting total sum of squares. Then the best split point and predictor variable is chosen, that is the split point (on a particular predictor) that induces the maximum reduction in the total sum of squares. Subsequently, the tree algorithm looks for the next best split, etcetera. Normally, a stopping rule is used that determines the minimal number of subjects in a terminal node. Moreover, Breiman et al. [20] developed a so-called pruning technique based on a cross-validation procedure to determine the best size of the tree (i.e. the best number of terminal nodes). For each size of the tree the cross-validated mean sum of squares is computed (called the cross-validated error). The best size is determined by the one standard error rule (formulas are given in Breiman et al. [20, pp 234, 237, 308]).

RTA consists of three phases. In the first phase, a linear main effects model is fitted with multiple regression. In the second phase, a small regression tree (called a 'regression trunk') is fitted with the residuals of the main effects model used as the outcome variable. The treatment variable is used for the first split of the regression trunk, because the focus is on interaction effects with this variable. In the third phase, the regression trunk is converted into dummy variables. Each dummy variable indicates a terminal node of the regression trunk. The dummy variables are added as a second step to the main effects model of the first phase. In this study, we used as a stopping rule a minimal terminal node size of 10% of N. The best RTA model was selected using leave-one-out cross-validation[2]. In this case, the best pruning rule for RTA is the following: choose the model with the smallest number of dummy variables that has a cross-validated error lower than or equal to the minimum cross-validated error plus 0.60 times the standard error. Results from a simulation study indicated that this rule has a reasonable Type I error ($\alpha = 0.05$), indicating that the risk of finding effects that are purely based on chance differences is low.

The Hierarchical Multiple Regression Approach (HMR) to ATI. We compared the RTA analyses to the results of HMR. The first step of the HMR analysis was similar to the first step of the RTA analysis. In the second step, cross-products were added between each of the two dummy variables (CTdum and ADdum) and after centring each of the LOC variables (i.e. eight products in total). A stepwise selection procedure was used to select significant cross-products, representing first-order ATI effects.

Testing. The final RTA model was fitted on the remaining nine outcome variables. Instead of pretest HAMA, the pretest measure of the outcome of interest was included in the first step. Because the panic frequency distribution was highly skewed, the pretest and posttest panic frequencies (plus 1) were transformed using the natural log in order to provide more normal distributions.

Results

Of the 137 participants, 3 were excluded from the analyses because of a missing value on posttest HAMA. Of the remaining 134 participants, 6 had missing values on each of the pretest LOC scales. For 1 of these 6 participants, we had scores on the posttest LOC scales, and we imputed these scores on the pretest LOC scales[3], the oth-

[1] The total sum of squares of the root node is given by

$$\sum_{i=1}^{N}(y_1-\bar{y})^2,$$

where $i = 1, ..., N$, and $\bar{y}$ is the mean of the outcome variable for the total sample N. After splitting, the total sum of squares in the left and right child node is given by

$$\sum_{i=1}^{n_l}(y_i-\bar{y}_l)^2+\sum_{i=1}^{n_r}(y_i-\bar{y}_r)^2,$$

where $\bar{y}_l$ is the mean of the outcome variable for the subjects in the left node (n_l) and $\bar{y}_r$ is the mean for the subjects in the right node (n_r).

[2] The analysis in this study differs from the one reported briefly previously [17]. The previous one did not include the placebo condition. Furthermore, in the present analysis leave-one-out cross-validation was used instead of tenfold cross-validation. The reason for this was that results from the more stringent leave-one-out procedure were consistent when replicated, whereas those from the tenfold procedure were not.

[3] This participant was in the pill-placebo condition. No significant differences were found in the placebo condition between pretest and posttest for three of the LOC scales. A significant difference was found for therapist LOC, but this variable appeared to be an unimportant predictor in the analyses.

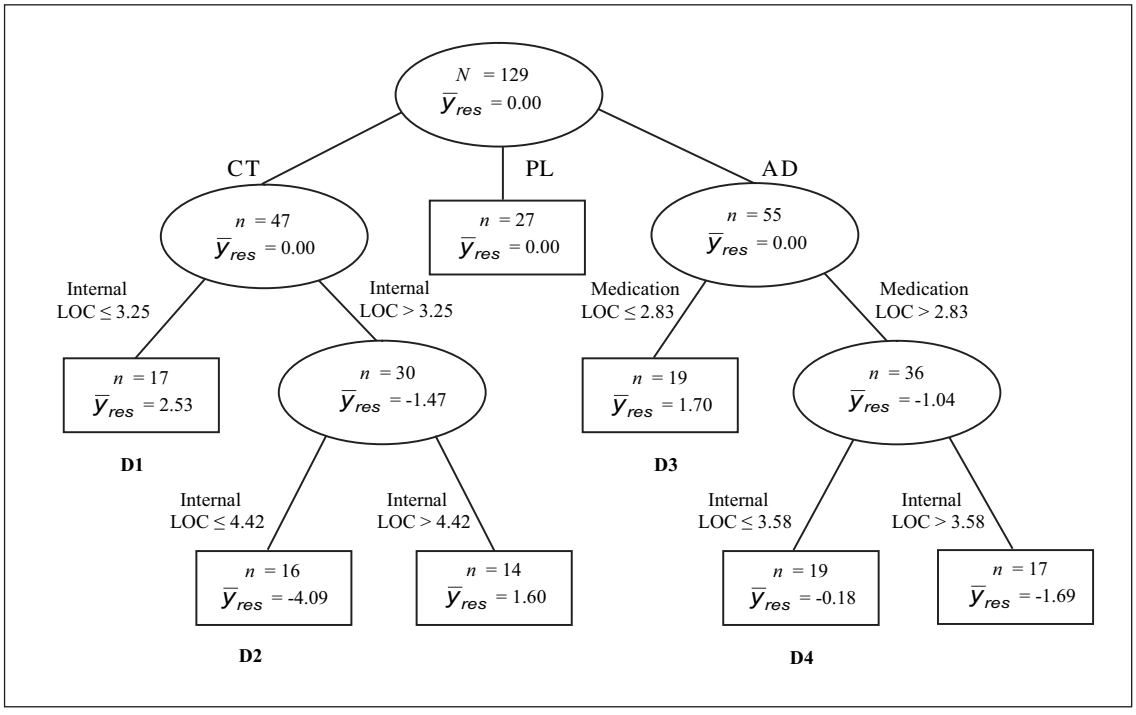

Fig. 1. Regression trunk for the total sample (N = 129) of panic disorder patients. The outcome variable is the residual of the linear main effects model ($\bar{y}_{res}$) for the posttest Hamilton Rating Scale for Anxiety. The number of patients and their mean value on the outcome variable are given in each node. CT = Cognitive therapy; AD = antidepressants; PL = placebo. Below the nodes, the labels of the corresponding dummy variables (D1, D4) are displayed. For example, patients were assigned a value 1 to D1, if they were in the CT condition and if their score on the internal locus of control scale was lower than 3.25. The other patients were assigned a value 0 to D1.

er 5 were excluded. The resulting sample size was 129 and the sample sizes per condition were: AD (n = 55), CT (n = 47), PL (n = 27).

The multiple regression model, including the main effects of pretest HAMA, CT, AD, duration, agoraphobia, chance LOC, internal LOC, medication LOC, and therapist LOC accounted for 29.5% of the variance in posttest HAMA. The fitted regression trunk is given in figure 1. Several dummy variables were computed using the terminal nodes of the regression trunk (D1–D4). We estimated the variance-accounted-for for all possible models with one, two, three, or four dummy variables (entered as a second step to the main effects model). From the models with the same number of dummy variables, we selected the model with the lowest apparent error (defined as $1 - R^2$). In table 1, the apparent error, the cross-validated error, and the corresponding standard errors of these models are shown. The RTA model with the minimum cross-validated error (0.772) included the main effects and two aptitude-treatment interaction effects (D2, D3). The more parsimonious RTA model, for which the 0.60 standard error rule holds ($0.786 \leq 0.772 + 0.60 \times 0.098$), included the main effects and one interaction effect between CT and internal LOC (D2). The variance-accounted-for by this model is 35.5%. The effect size of the interaction was 0.09, indicating a medium effect size [21]. The regression coefficient of the interaction term was negative, meaning that for patients with a medium value on internal LOC (between 3.25 and 4.42; see fig. 1) CT was superior to pill-placebo. We will refer to this model as the final RTA model[4].

[4] We performed additional analyses using two imputed datasets (n = 134); for the five participants with missing values on the LOC scales, we imputed in the first dataset a 6 on the internal LOC scale and a 1 on the remaining LOC scales, and in the second dataset a 1 on the internal LOC scale and a 6 on the remaining LOC scales. The RTA analysis for these datasets resulted in the same left side of the regression trunk shown in figure 1. This reassured us that the missing data points do not influence the nature of the threshold interaction effect included in the final RTA model.

Table 1. Prediction error of regression models for posttest Hamilton Rating Scale for Anxiety, differing in number of threshold interaction terms (N = 129)

Method	Model	Apparent error (SE)	CV error (SE)
Multiple regression	main effects[a]	0.705 (0.079)	0.835 (0.094)
Regression trunk Approach[b]	main + D2	0.645 (0.077)	0.786 (0.095)
	main + D2 and D3	0.626 (0.079)	0.772 (0.098)
	main + D2, D3, and D4	0.622 (0.078)	0.781 (0.100)
	main + D1, D2, D3, D4	0.618 (0.078)	0.813 (0.106)

Apparent error = $1 - R^2$; SE = standard error; CV error = error determined by leave-one-out cross-validation.

[a] The main effects model included the following predictors: pretest Hamilton Rating Scale for Anxiety, CTdum (cognitive therapy vs. placebo), ADdum (antidepressants vs. placebo), duration of panic disorder, pretest agoraphobia, internal locus of control (LOC), chance LOC, medication LOC, and therapist LOC.

[b] The dummy variables D1, D2, D3, and D4 represent threshold interactions. Their meaning can be derived from figure 1.

Table 2. Standardized regression coefficients of the final model, including one threshold interaction (D2), estimated for all outcome measures

Predictors	Outcome measures									
	pan. freq.	CGI	PGE	HAMA	MSPS-anx.	MSPS-ago.[a]	OPh	AAS	SDS	MADR
Pretest	0.51*	0.15	0.14	0.19*	0.30*	n.a.	0.26*	0.26*	0.34*	0.23*
Duration	0.08	–0.01	0.10	0.23*	0.07	0.06	0.05	–0.04	0.03	0.23*
Agoraphobia	0.12	0.21*	0.07	0.09	0.39*	0.69*	0.21*	0.26*	0.16	–0.01
ADdum	–0.40*	–0.58*	–0.54*	–0.41*	–0.33*	–0.28*	–0.53*	–0.54*	–0.46*	–0.37*
CTdum	–0.29*	–0.17	–0.27*	–0.02	–0.02	–0.06	–0.10	–0.21	–0.09	0.15
Internal LOC	–0.13	–0.05	–0.04	–0.16	–0.09	–0.04	–0.09	–0.09	–0.01	–0.14
Chance LOC	0.03	0.00	0.01	0.04	–0.02	0.04	0.03	–0.02	0.11	0.07
Medication LOC	0.02	0.27*	0.21*	0.24*	0.17*	0.16*	0.28*	0.22*	0.27*	0.26*
Therapist LOC	–0.09	–0.10	0.00	–0.03	–0.01	–0.03	–0.03	–0.07	–0.04	0.00
CT and internal (D2)	–0.05	–0.21*	–0.25*	–0.29*	–0.19*	–0.17*	–0.23*	–0.22*	–0.11	–0.19*

Pan. freq. = Panic frequency; CGI = CGI severity of illness; PGE = patient global evaluation; HAMA = Hamilton Rating Scale for Anxiety; MSPS-anx. = anxiety scale of Marks-Sheehan phobia scale; MSPS-ago. = agoraphobia scale of Marks-Sheehan phobia scale; OPh = overall phobia score; AAS = anticipatory anxiety score; SDS = Sheehan disability scale; MADR = Montgomery-Asberg depression rating scale; duration = duration of panic disorder; agoraphobia = pretest MSPS-ago.; ADdum = antidepressants vs. placebo; CTdum = cognitive therapy vs. placebo.

[a] In the prediction model for posttest MSPS-ago., the pretest measure is equal to agoraphobia, therefore, this predictor is included only once.

* Two-tailed $p \leq 0.05$.

The classical approach with a stepwise selection procedure resulted in a model including main effects only. In other words, no interaction terms (computed as cross-products) were selected in the final multiple regression model using either forward or backward selection. Because the threshold interaction found by RTA incorporated a nonlinear effect of internal LOC by selecting only the persons with a medium level, we also investigated whether this type of interaction effect could have been discovered when modelling it as a product between CTdum and a qua-

dratic term of internal LOC, that is, as a curvilinear by linear interaction. However, this was not the case.

The final RTA model indicated that only one stable aptitude-treatment interaction was present: between CT and internal LOC (represented by dummy variable D2). We tested if this interaction effect was also significant for the other outcome measures, after accounting for the linear main effects (table 2). The regression coefficient of dummy variable D2 was significant for 8 of the 10 outcome variables.

Discussion

Our results suggest a differential effect of cognitive therapy (CT), predicted by internal locus of control (LOC). Especially panic disorder patients with a medium internal LOC appeared to benefit from CT. They performed, on average, better on eight of the ten outcome variables than patients who received pill-placebo treatment; patients with a high or low internal LOC who received CT performed similarly to patients who received pill-placebo. No interaction effect was found for the other subscales of LOC: medication, chance, and therapist LOC. Also, no differential effect of antidepressant treatment (AD) was found. All patients who received AD performed better than patients who received pill-placebo.

Our study is a first attempt to investigate predictors of the differential effectiveness of panic disorder treatments and the results confirm our hypotheses only partly. The results indicate that the hypothesis that patients with a low internal LOC benefit less from CT has to be refined. Patients with a low internal LOC responded indeed worse to CT than those with a medium internal LOC, but they responded in the same way as those with a high internal LOC. We could not confirm our hypothesis that patients with a high medication LOC will benefit more from antidepressants. Furthermore, in contrast to previous findings [14, 15], we found that patients with a medium LOC profited more from a cognitive behavioral treatment versus a placebo treatment, instead of patients with a high LOC. A plausible cause for the difference in results between our study and the study of Reich and Zautra [15] is the difference in 'control' condition. We used a pill-placebo condition, while Reich and Zautra [15] used a placebo-contact condition. A possible explanation for the incongruity with the finding of Liberman [14] is the construction of 'low, medium, and high internals'. We used an optimal categorization of locus of control into three categories. The cut-off points were optimized with respect to the variance-accounted-for. Liberman took the top third as high internals and the bottom third as low internals. The medium category was disregarded in further analyses. When applying the approach of Liberman to our data, we found a trend interaction effect ($p = 0.09$) indicating that in the CT condition high internals performed better than low internals whereas in the pill-placebo condition low internals performed better. This result corresponds to the finding of Liberman. Apparently, the way of categorization influences the results highly. A V-shaped curve approximated our data the best; the RTA categorization, with cut-off points 3.25 and 4.42, seemed to do more justice to the shape of the curve than the Liberman categorization, with cut-off points 3.05 and 3.99.

In general, one might argue whether categorization of a continuous variable is needed anyway. We think that such a categorization is desirable, because our long-term goal is to investigate whether variables such as the internal LOC variable can be used as a prescriptive variable [5] in clinical practice, that is, one that prescribes whether CT is an appropriate treatment for a panic disorder patient. We should notice, however, that the cut-off points we found on internal LOC are determined on one, relatively small, sample. Replication of the results in a larger sample is needed to test whether the cut-off points are meaningful and whether the conclusion that especially patients with a medium internal LOC profited from CT is confirmed.

We propose the following explanation for the differential effect of CT for patients differing in their internal LOC. Patients having a high internal control orientation may have the expectation that they can handle panic attacks by themselves, but may be more easily discouraged or disappointed if panic attacks 'out of the blue' do not readily disappear in spite of their efforts to apply CT. Patients with a medium internal control orientation possibly have a more realistic view of their own ability to manage their panic attacks, which will, in combination with learning how to use self-management skills in CT, result in a lower level of posttreatment anxiety.

A limitation of the present study is that we focused only on LOC as a patient characteristic that possibly influenced the effectiveness of the treatments. We acknowledge that LOC may be correlated with other patient characteristics that are the actual predictors of change within treatment groups. Examples of such characteristics are: self efficacy [9], ego strength, perfectionism, and readiness to change [5], and past therapy experiences.

Our data suggest that panic disorder patients respond differently to cognitive therapy. The present data need replication in larger samples, but it is conceivable that a division into high, medium and low LOC may contribute to a better prediction of outcome in panic disorder patients treated with cognitive therapy. It would be interesting for future research to investigate predictors of differential effects of other panic disorder treatments, for example, internet-guided self-help with self-exposure instructions [22]. We would like to stimulate treatment effectiveness research to abandon the idea of a best treatment for every panic disorder patient, and to investigate the influence of patient characteristics on the effectiveness of different types of panic disorder treatments.

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