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THE ROLE OF ALEXITHYMIA AND GASTROINTESTINAL-SPECIFIC ANXIETY AS PREDICTORS OF TREATMENT OUTCOME IN IRRITABLE BOWEL SYNDROME

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Abstract

In a previous investigation irritable bowel syndrome (IBS) was associated more to alexithymia than gastrointestinal-specific anxiety (GSA). In this study their independent contribution in predicting treatment outcome was longitudinally investigated. Consecutive 150 IBS patients were evaluated for IBS symptoms, alexithymia, GSA, and psychological distress with validated scales after as-usual treatment for 6-12 months. The primary treatment outcome was improvement measured with the IBS-Severity Scoring System that showed 111 patients who improved and 39 who did not improve. Improvement was associated to both alexithymia (d=1.27) and GSA (d=4.63) but only alexithymia showed overtime stability by hierarchical regression, controlled for co-variables. A series of logistic and linear regressions showed that baseline alexithymia, but not GSA, independently predicted both post-treatment improvement status (Cox & Snell R^2=0.15; overall classification rate = 74%) and symptom change (23% of explained variance). Although alexithymia and GSA were closely related IBS symptoms, only alexithymia was found to be a stable trait and a stronger predictor of treatment outcome than GSA. Since no treatment was established to be definitely effective for IBS, clinicians might improve treatment outcome by identifying patients with high alexithymia, attempting to improve their coping skills, emotional regulation, and affective awareness.

Keywords: Alexithymia; Gastrointestinal-specific Anxiety; Irritable Bowel Syndrome; Treatment Outcome

Abbreviations: *DIF* = Difficulty Identifying Feelings; *DDF* = Difficulty Describing Feelings: *EOT* = Externally Oriented Thinking; *FGID* = Functional Gastrointestinal Disorders; *GSA* = Gastrointestinal-specific Anxiety; *GSRS-IBS* = Gastrointestinal Symptom Rating Scale-IBS; *HADS* = Hospital Anxiety and Depression Scale; *IBS* = Irritable bowel syndrome; *IBS-SSS* = IBS Severity Scoring System; *TAS-20* = Toronto Alexithymia Scale-20; *VSI* = Visceral Sensitivity Index.

HIGHLIGHTS

- The role of GSA and alexithymia in treating IBS was investigated.
- Alexithymia but not GSA showed overtime stability.
- Alexithymia was a stronger predictor of IBS treatment than GSA.
- Alexithymia should be assessed before treating IBS patients.

1. Introduction

Alexithymia is a multifaceted personality dimension defined as a reduced ability to identify and describe subjective feelings and to distinguish among different feelings, a paucity of fantasy, and a concrete cognitive style [1]. These characteristics are thought to reflect deficits in the cognitive processing and regulation of emotions that affect health [2], including somatization [3]. In the last 40 years consistent evidence has been shown for high levels of alexithymia in a large number of functional and organic conditions as skin, cardiovascular, kidney, respiratory, oncologic, neurologic, endocrinology, and immune diseases (for a review, see [4]). Alexithymic deficits can affect health perception through dysregulation of stress-related autonomic arousal, low tolerance to painful stimuli, somatosensory amplification, high health care utilization, and posttraumatic shutdown of emotions [2,4]. Finally, neuroimaging evidence shows that alexithymia is associated with reduced neural responses to emotional stimuli from the external environment and activity during imagery in limbic regions (e.g., amygdala and cingulate cortex) and, in contrast, is associated with enhanced neural activity in somatosensory and sensorimotor regions, including the insula [5].

Not surprisingly, alexithymia has been related to functional gastrointestinal disorders (FGID), a group of disorders currently conceptualized as altered communication of the bidirectional gut-brain axis that are not explained by known structural or organic abnormalities [6,7]. Earlier findings in these patients showed that alexithymia is prevalent at 43% to 66% [8-12], was associated to chronic fatigue through depression and somatization [13], and predicted functional symptoms independently of the presence of organic diseases as inflammatory bowel disease [14], gallstone disease [15], endoscopic findings [9], and chronic hepatitis C [16]. Finally, alexithymic patients with irritable bowel syndrome (IBS) showed visceral hypersensitivity (emotional and autonomic hyperarousal in response to interoceptive unpleasant visceral sensations, particularly stronger pain and urgency for defection) and higher activity in the right insula – which is the primary projection area for visceral afferent information and is critically involved in subjective emotional experience and awareness of

the internal bodily state – and orbital gyrus – which receives robust sensory inputs and acts as an internal environmental integrator that coordinates behavioral, autonomic, and endocrine responses in response to colonic distension [17].

IBS is one of the most prevalent FGIDs in which abdominal pain is associated with defecation or a change in bowel habit (diarrhea and/or constipation and related problems of abdominal gas, abdominal distension, flatulence, poor digestion) [18]. It has a chronic relapsing course, with 12-15% prevalence [19], and is associated with impairment of quality of life, psychosocial functioning and considerable socioeconomic burden because of high direct and indirect costs [20]. Some psychological factors have been found to affect visceral symptom perception in IBS patients (for a review, see [21]), including GI-specific anxiety (GSA). GSA refers to the cognitive, affective, and behavioral response stemming from fear of GI sensations or symptoms, and the context in which these visceral sensations and symptoms occur [22-24]. It is focused specifically on the IBS core features (abdominal pain and altered bowel habit) in specific contexts as situations involving food and eating, like restaurants and parties or locations in which bathroom facilities are not known or difficult to reach. Briefly, GSA relates to hypervigilance to, and fear, worry, and avoidance of GI-related sensations and contexts [24], thus contributing to more severe IBS symptoms, psychological distress, and poor quality of life [22].

Alexithymia and GSA are likely involved in visceral symptom perception since they may indicate difficulty in emotional regulation, biased selective attention to somatic sensations, higher negative emotionality, exaggerated symptom reporting, poor coping, avoidant behaviors, higher health anxiety resulting in heightened fear of GI symptoms (GSA) and difficulty identifying and describing feelings (alexithymia). In a previous cross-sectional investigation [25] we found that, although GSA and alexithymia were closely related to each other and to IBS –suggesting a common basis of emotional dysregulation underlying the clinical manifestations of IBS –, alexithymia was a stronger predictor of symptom severity than GSA. The aim of this follow-up study was to investigate in the same patient sample the independent role of stable traits of GSA and alexithymia

in predicting response to 6-12 months of as-usual treatment. More specifically, we investigated whether symptom improvement (defined as clinically significant positive change of IBS symptoms from pre- to post-treatment) could be independently predicted by the level of alexithymia and GSA, over and above clinical and psychological cofactors. Based on previous literature, we expected that both constructs would be related to the treatment outcome. However, since to our knowledge this is the first longitudinal study investigating alexithymia and GSA jointly, we could not expect which of them would be more determinant in treating IBS patients.

2. Methods

2.1 Patients

As previously reported [25], participants were consecutive adult outpatients (18-70 years-old) referred for their first time to our Institute, a GI tertiary care hospital in southern Italy, and fulfilling Rome III diagnostic criteria for IBS [18]. Patients with comorbid organic GI disease (e.g., inflammatory bowel disease), severe medical comorbidity (e.g., cancer, ischemic heart disease, metabolic disease, or autoimmune disease), pregnancy, mental retardation, current or past diagnosis of schizophrenia or other psychotic disorders, and current substance abuse were excluded. Patients were evaluated for medical history and past or current psychopathology by senior investigators. All patients gave written informed consent to participation. The study was approved by the local Ethics Committee.

Patients were treated on a case-by-case basis with combination and variable forms of GI and/or psychotropic medications, diet modifications, and psychological counseling or brief psychotherapy. They were re-evaluated after a period of treatment ranging from 6 to 12 months based on the clinical course of IBS. The period of treatment was not pre-established to maximize the ecological validity of the trial and make the study as closer as possible to clinical reality.

2.2 Measures

2.2.1 GI-specific anxiety

GSA was measured with the Visceral Sensitivity Index (VSI) [23,24], a 15-item self-report questionnaire designed to measure those unique aspects of fear, anxiety, and hyper-vigilance that can accompany misappraisals of visceral sensations and discomfort and the context in which these occur. The VSI includes a six point response scale yielding a range of possible scores from 0 (no GSA) to 75 (severe GSA). Although it measures five different dimensions of GI-related cognitions and behaviors (fear, worry, vigilance, sensitivity, and avoidance), the VIS is a mono-dimensional scale. Even though the 5 domains were included in the item scale contents, validation studies showed the scale has no distinct factors that can be evaluated independently, thus resulting in a global single score. It has however shown excellent psychometric properties, including concurrent, divergent, and discriminant validity [24].

2.2.2 Alexithymia

Alexithymia was assessed with the 20-item Toronto Alexithymia Scale (TAS-20) [26,27] which is comprised of 20 items rated on 5-point Likert scales. In addition to the total score, the TAS-20 yields scores for three factor scales: difficulty identifying feelings (DIF), difficulty describing feelings (DDF), and externally oriented thinking (EOT). Subjects scoring higher than 60 to the total scale are considered in the higher levels of the alexithymia range. The scale is considered the standard measure for alexithymia because of its psychometric properties of internal consistency, construct validity, and factor structures that has been shown worldwide [28].

2.2.3 IBS symptoms

Symptoms of IBS were evaluated with the Gastrointestinal Symptom Rating Scale-IBS (GSRS-IBS), a validated self-assessment instrument to assess symptoms of IBS [29]. It includes 13 items, each using a Likert scale (0–6 points), that are grouped into symptom clusters of bloating, diarrhea, constipation, abdominal pain, and satiety. The GSRS-IBS has shown high internal consistency

reliability, good construct validity when compared with similar constructs and various health-related quality of life scores, and satisfactory sensitivity to change [29].

2.2.4 IBS severity index

Severity of IBS was assessed by using the Irritable Bowel Syndrome Severity Scoring System (IBS-SSS) [30]. It is based on perceived severity of pain, number of pain days, severity of abdominal distension, satisfaction with bowel habit and subjective interference over the previous 10 days. Each of these questions generates a maximum score of 100 using prompted visual analogue scales. Scores generated for each of these modalities are summed up to obtain the final severity score ranging from 0 to 500 (higher score = higher severity). The IBS-SSS has been widely used as external criterion for establishing severity of IBS in literature [31].

2.2.5 Psychological distress

Psychological distress was assessed with the Hospital Anxiety and Depression Scale (HADS) [32], a 14-item self-report scale composed of two 7-item scales for anxiety (HADS-A) and depression (HADS-D), that is specifically designed for medical patients. Scores may range from 0 (absence of symptoms) to 21 (highest symptoms) in each scale. The HADS has been widely used in various medical settings, including gastroenterology, and demonstrated good reliability and validity [33].

2.3 Outcome criteria

A major problem with prospectively designed studies of IBS is the lack of consensus on how to measure outcome. The Rome III panel of experts has indicated the preference for an *apriori* definition of responder reflecting meaningful clinical symptom improvement and the IBS-SSS as the best integrative scale for measuring adequate symptom relief, provided with evidence of good face, construct, and criterion validity, reliability, and sensitivity to treatment effects [34]. In the

present study, the IBS-SSS score was used to categorize patients into improved and unimproved outcome groups. Adopting the recommended cutoff levels [31], a score change of at least 50 was considered adequate to detect improvement.

Since patients with higher symptom severity are likely to be enrolled in IBS intervention studies and may inevitably improve after a given period of time, to minimize the bias of regression to the mean we calculated also the change of symptom severity, expressed as the proportion of change from pre- (T1) to post-treatment (T2) and calculated as follows: (IBS-SSS score at T2 *minus* the IBS-SSS score at T1) / IBS-SSS score at T1.

Secondary outcomes were considered the level of IBS symptoms (GSRS-IBS) and psychological distress (HADS).

2.4 Statistical analysis

Between-group differences in scores of continuous and categorical variables were evaluated with two-tailed independent and paired-sample t and χ^2 tests. Associations between variables were evaluated with unilinear regression (Pearson's r). Effect sizes were expressed as standardized mean differences. A standardized effect size (Cohen's d) of 0.20-0.50 is considered small, 0.50-0.80 moderate, and >.80 large.

A two-step strategy was adopted. First, the overtime stability of GSA and alexithymia was investigated. Stability of GSA and alexithymia was analyzed by distinguishing between absolute and relative stability. Absolute stability, or change of psychological scores over time, was evaluated by comparing mean scores from T1 to T2 with two-tailed, paired-sample t tests. Relative stability, or the degree to which the relative differences among individuals remain the same over time, was analyzed with two procedures. First, the Pearson product-moment correlation of scale scores between T1 and T2 were used as measures of association. Second, a series of multiple regression models examined the extent to which stability in alexithymia (TAS-20) and GSA (VSI) as dependent (criterion) variables may be accounted for by individual differences in psychological

distress (HADS) and IBS symptoms (GSRS-IBS) as predictors in improved and unimproved patients. Overtime stability is relevant for this investigation because it establishes the degree to which the relative differences among individuals remain the same over time (relative stability), even though scores may change (absolute changes) or remain stable (absolute stability) over time. Assessing overtime stability at a relative level is sufficient to establish whether a personality dimension is a vulnerability factor for certain health problems and a moderator of their response to treatment, as previous data suggest for alexithymia [2,4] whereas no data are available for GSA at this time.

The second step was constituted by investigating the ability of the two psychological constructs to predict the treatment outcome by using logistic regression in which the treatment outcome (improvement/unimprovement) served as the dependent (criterion) variable and TAS-20, HADS, VSI, and GSRS-IBS scores at T1 and T2 as the independent (predictor) variables. In hierarchical regression, the proportion of change in IBS-SSS score from T1 to T2 served as dependent (criterion) variables and the same scales as in the logistic regression as predicting variables. Semipartial correlation coefficients (i.e., correlations between the dependent variable and each independent variable, after removing the common variance from the predictor only) were used to facilitate comparisons across predictors on the same scale.

All statistical analyses were run under the Statistical Package for Social Sciences software (SPSS, version 18.0 for Windows). The level of significance was set at 95%.

3. Results

3.1 Characteristics of the patients

As reported earlier [25], 177 (91.2%) of the screened patients were included, without any significant difference between recruited and excluded patients for socio-demographic and GI variables. Of the 177 included patients, 25 (14.1%) were lost to follow-up, thus leaving 150 for the present investigation. Once again, no baseline difference was found between included and dropped

patients for any variable. The final sample of 150 patients (72% women) had mean age of 34.4 years (SD=12.1; range 18-62) and mean education of 12.4 years (SD=3.5; range 8-18). Most patients co-lived (*n*=72, 48%) or were married (*n*=66, 44%). Mean duration of illness was 41.9 months (SD=50.3; median=24; range 10-480) and 22 (14.7%) patients satisfied criteria for another gastroesophageal functional disorder. All patients had moderate (IBS-SSS=175-300) or severe (IBS-SSS>300) symptoms. No between-gender differences were found for socio-demographic variables and illness duration.

Patients were treated for 6 to 12 months (mean=8.3, SD=2.4) on a case-by-case basis. The improved group (IBS-SSS≥50) was comprised of 111 patients (30 men and 81 women; mean age=32.8 years, SD=11.0; mean education=12.5 years, SD= 3.5) and the unimproved group (IBS-SSS<50) of 39 patients (12 men and 27 women; mean age=38.8 years, SD=13.9; mean education=12.1 years, SD=3.5). After treatment, 87 (87.4%) improved patients had no (IBS-SSS<75) or mild (IBS-SSS=75-175) symptoms whereas all unimproved patients remained in the same IBS symptom severity category as at baseline. Improved patients were older ($t_{(148)}$=2.74, *p*=.007) than unimproved patients whereas gender and education were not significantly different between the two groups.

3.2 Absolute and relative stability of GSA and alexithymia

For assessing absolute stability, namely the change of psychological scores over time, improved and unimproved patients were compared at T1 and T2 (Table 1).

- Please insert Table 1 about here -

Consistently, in both groups there were significant pre-post score differences with large effect sizes in the expected directions. In within-subject pre-post comparisons, the TAS-20 showed effect sizes in the small range in the improved group (*d*=0.40) whereas no significant change was observed in the unimproved group (*d*=0.06). VSI was associated largely with improvement (*d*=2.52) and moderately high with unimprovement (*d*=0.73) while TAS-20 only moderately with

improvement (d=0.40). As expected, most scales significantly correlated to each other (supplementary Table S1).

Overall, these findings suggest that alexithymia was associated to IBS severity in the context of symptom change whereas GSA was closely related to IBS severity regardless of the period of assessment.

Test-retest reliability showed overall high relative stability of both constructs (supplementary Table S1). Another procedure that can be conducted to assess the relative stability of personality traits, especially in treatment outcome studies which typically involve substantial change in symptom severity, is hierarchical regression [35]. In the first regression model, post-treatment alexithymia served as criterion and baseline TAS-20 as well as the other T1 and T2 scale scores as independent variables in separate blocks (Table 2).

- Please insert Table 2 about here -

Using the total sample, controlled for IBS symptoms, GSA, HADS, and baseline TAS-20 significantly predicted alexithymia at T2 (R^2=0.53, semipartial r=0.39) to which VSI (particularly at T2, semipartial r=0.31, than T1, semipartial r=0.04) added 12% of explained variance. A similar pattern of results emerged in the improved and the unimproved groups (supplementary Table S2).

In the second regression model, VSI scores at T2 served as criterion and baseline VSI as well as the other T1 and T2 scale scores as independent variables in separate blocks (Table 3).

- Please insert Table 3 about here -

In the total sample, baseline VSI was independently predicted mostly by TAS-20 ($R^2change$=0.36) and GSRS-IBS (particularly at T2: R^2 *change*=0.39), adjusted for co-variables. The contribution of baseline VSI in predicting VSI at T2 was minimal (R^2=0.12), after adjustment for co-variables. Also in the two outcome groups separately, VSI at T2 was almost mostly predicted by TAS-20 (supplementary Table S3).

Overall, these results suggest that any association between related variables and TAS-20 scores cannot account for the stability of TAS-20 scores across the treatment period while substantially no relative stability was found for VSI in the context of treatment effects. Thus, TAS-20 scores can be seen as a reliable and stable variable for predicting treatment outcome.

3.3 Predicting treatment outcome

Having established the overtime stability of alexithymia, a series of logistic and linear regression analyses were performed next to determine if TAS-20 can predict the treatment outcome. For the logistic regressions, treatment outcome (improved/unimproved) served as criterion and TAS-20, HADS, VSI, and GSRS-IBS scores at T1 as independent variables. Among sociodemographic factors, only age was included in the regression model as control variable because it significantly differentiated the two treatment outcome groups.

Each of the independent variables was entered as single predictors in separate blocks to determine how well each variable alone predicted treatment outcome (Table 4).

- Please insert Table 4 about here -

Baseline GSRS-IBS and TAS-20, but not VSI, significantly and independently predicted the treatment outcome. In particular, GSRS-IBS significantly explained about 1% of variance while TAS-20 alone added 10% of explained variance. The final model accurately predicted 89% of the improved and 61% of the unimproved patients (overall classification rate = 74%). By removing TAS-20, the model explained 8% of the criterion variance and GSRS-IBS was the only variable significantly associated to the treatment outcome, adding 5% to the explained variance (B=0.079, p=.007) (data not shown).

In the subsequent hierarchical regression, the proportion of change in IBS-SSS scores from T1 to T2 served as criterion (higher score = more improvement). Using the same modeling procedure as the logistic regression analyses, age and baseline GSRS-IBS, HADS, VSI, and TAS-20 scores were entered as single predictors in separate blocks to determine how well each of these independent

variables alone was able to predict treatment outcome considered as change in IBS severity (supplementary Table S4). The final model predicted 23% of the explained variance. After controlling for co-variables, TAS-20 scores emerged as the unique significant predictor of treatment outcome, adding 17% of explained variance of change in IBS severity symptoms after treatment (semipartial r=-0.41). As with the logistic regression model, by removing TAS-20, GSRS-IBS uniquely predicted the change of IBS severity (R^2=0.07) (data not shown).

Logistic and hierarchical regressions were replicated by using the same modeling procedure and replacing TAS-20 with single factor scores (see Tables 4 and S4). Results did not change substantially when baseline DIF and DDF were entered as predictors while the EOT factor did not enter the final models.

4. Discussion

Alexithymia and GSA contribute to the development of IBS and may represent relevant factors for treatment. A wide body of literature (see reviews in [18, 21]) has shown that multiple factors contribute indeed to IBS pathogenesis; several successful treatment options are available but no single approach is likely to obtain definite and stable recovery; treatment outcomes rely basically on subjective symptom perception; and the cognitive processing of emotional and visceral stimuli may determine whether somatic sensations should receive clinical attention, how they influence quality of life and, eventually, the criterion on which establishing therapeutic outcomes [36]. Actually, the subjective perception of IBS symptoms can be largely influenced by the inability to distinguish subjective feelings from emotional arousal and somatic sensations (i.e., alexithymia) [8-12] and heightened attention to visceral sensations leading to increased worry and fear of GI-related contexts (i.e., GSA) [22,37,38]. In a previous cross-sectional study [25] we found in moderate-to-severe IBS patients that, although both contributed to symptom severity, alexithymia was a stronger predictor than GSA. Because of the cross-sectional study design, the overtime influence of these two psychological constructs on symptoms and response to treatment could not be ascertained.

In the present study those patients were followed up for 6 to 12 months of as-usual treatment (including psychological interventions alone or combined with medical therapy) and, for the first time to our knowledge, the independent contribution of alexithymia and GSA to treatment outcome was investigated. Overall, 3/4 of patients obtained clinically significant improvement in each intestinal functioning domain (abdominal bloating, altered bowel movements or diarrhea/constipation, abdominal pain, and early satiety) (see effect sizes in Table 1). Of note, IBS patients who had more severe symptoms at baseline and did not improve after treatment showed a further worsening of symptoms, particularly unpleasant sensation of gas bloating and abdominal pain (see effect sizes in the unimproved group in Table 1). As expected, consistent with earlier treatment investigations on alexithymia in FGID [39] and non-GI disorders [40-42] as well as GSA [43,44], responding patients showed lower levels of post-treatment alexithymia and GSA compared to baseline. However, compared to GSA, alexithymia evidenced two specific features within this sample. First, alexithymia showed overtime stability, consistently with literature suggesting relative stability within the context of change of symptoms following treatment [45,46]. In contrast, GSA showed no overtime stability and was strictly related to symptom severity, likely in a bidirectional way. Second, alexithymia emerged as the most powerful predictor of treatment outcome, after controlling for GSA, IBS symptoms, and psychological distress. Since this is the first study investigating jointly the independent predictive role of alexithymia and GSA, our results cannot be compared with literature and call for further investigations.

Some potential pathways by which alexithymia might influence treatment outcomes in IBS can be hypothesized. First, alexithymic characteristics may foster the tendency to amplify and misinterpret the somatic sensations that accompany states of emotional arousal [2,4], thus reporting subjective poor health perception and lower self-reported response to treatment, as it may be expected in psychosomatic patients with somatosensory amplification [47]. Second, alexithymia may be involved in heightened pain perception because of altered brain processing of afferent signals within the brain-gut axis that characterized IBS [48]. Neural correlates of alexithymia have

been identified in pain-related brain areas, particularly increased activity of cingulate cortex and insula (involved in emotional processing and mapping bodily states) and decreased activity of amygdala and dorsolateral prefrontal cortex (involved in reduced attention to emotional salience, affective evaluation of emotional stimuli, and emotional regulation) [5,49]. The modulation of activity in those brain areas may explain the close relation between higher alexithymia and heightened visceral sensitivity to induced colon distension [17]. Third, unhealthy behaviors such as poor nutritional consumption, poor eating behavior, substance abuse, and a sedentary lifestyle, that likely worsen IBS symptoms [18], can be conceptualized as maladaptive efforts to self-regulate distressing affects in the alexithymia theoretical framework [2]. In large population surveys, alexithymia was found indeed to associate to maladaptive unhealthy behaviors (smoking, alcohol consumption, physical inactivity, low-density cholesterol, body mass index, blood pressure) leading to poor psychosocial adjustment and even increased mortality, over and above known risk factors [50,51]. Finally, alexithymia – particularly the facets of identifying and communicating feelings – was associated with poor outcome in our sample as well as in other studies (for a review, see [52, 53]). Higher levels of alexithymic features may elicit negative affective reactions from the therapist, from boredom to frustration when facing with individuals showing deficiency in expressing their inner feelings states within the context of a therapeutic relationship. In our sample, the DIF and DDF subscales of the TAS-20 were indeed the major factors predicting treatment outcomes and these aspects of the clinical encounters may have interacted with the therapist's implicit negative feelings and partially contribute to the poor outcome experienced by such patients. Even though not all patients within this sample underwent traditional psychotherapy, all of them received psychological counseling and support and therefore unwanted negative feelings from the therapist might have contributed to unimprovement.

4.1 Limitations

This study has several limitations. First, alexithymia and GSA were assessed with self-report scales. Particularly for alexithymia, a multimethod assessment including facets of the constructs from other sources of data (as clinician ratings, by-proxy information, and implicit motives) would be preferred, although more difficult to use in clinical settings (for a review, see Lumley et al, [45]). However, evidence strongly supports that the TAS-20 captures the core dimensions of the construct (impairment in experiencing and describing feelings), so that this self-report scale can be considered a valid and sound measure of alexithymia [54]. Second, relevant biomedical data as low-grade inflammation, immune modulation, or altered microbiota [55] were not controlled for and should be taken into account in future investigations. Third, high rates of psychiatric disorders have been consistently found in IBS patients [56]. We cannot exclude that comorbid psychopathology may have had a mediating effect on treatment outcome. Fourth, treatment outcomes were evaluated at the end of 6 to 12 months of treatment and a follow-up assessment would be required because of the wax-and-wane nature of IBS course. Finally, IBS patients were recruited from a tertiary care clinic and had moderate to severe IBS severity. Therefore they may represent the most severe end of IBS severity continuum in which high levels of psychological problems, including alexithymia and GSA, may be prevalent [18]. The generalizability of our findings to IBS patients in primary care need to be established.

5. Conclusion

Alexithymia was found a stable trait and an independent and stronger predictor of treatment outcome than GSA in moderate to severe IBS. No treatment has been shown to be definitely effective for IBS and multicomponent therapeutic strategies are usually employed [57]. Therefore the clinical relevance of the present findings is that clinicians might improve treatment outcome for IBS patients by identifying those patients who are high in alexithymia and attempting to improve their coping skills, emotional regulation, and affective awareness.

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Table titles and legends

Table 1. Comparisons of GI-specific anxiety (VSI), alexithymia (TAS-20), IBS symptoms (GSRS-IBS), and psychological distress (HADS) before (T1) and after (T2) treatment in improved and unimproved groups.

Table 2. Hierarchical regression model predicting alexithymia (TAS-20) at T2 from baseline TAS-20 and T1 and T2 IBS symptoms (GSRS-IBS), GSA (VSI) and psychological distress (HADS) in the total sample.

Table 3. Hierarchical regression model predicting GSA (VSI) at T2 from baseline VSI and T1 and T2 IBS symptoms (GSRS-IBS), alexithymia (TAS-20) and psychological distress (HADS) in the total sample.

Table 4. Individual variable logistic regression predicting treatment outcome.

Supplementary tables

Table S1. Cross-correlations among scale scores at T1 and T2.

Table S2. Hierarchical regression models predicting alexithymia (TAS-20) at T2 from baseline TAS-20 and T1 and T2 IBS symptoms (GSRS-IBS), GSA (VSI) and psychological distress (HADS) in the improved and unimproved groups.

Table S3. Hierarchical regression models predicting GSA (VSI) at T2 from baseline VSI and T1 and T2 IBS symptoms (GSRS-IBS), alexithymia (TAS-20) and psychological distress (HADS) in the two outcome-related samples.

Table S4. Hierarchical regression predicting proportion of change in IBS-SSS scores.

Table 1. Comparisons of GI-specific anxiety (VSI), alexithymia (TAS-20), IBS symptoms (GSRS-IBS), and psychological distress (HADS) before (T1) and after (T2) treatment in improved and unimproved groups.

	Improved group (N = 111)				**Unimproved group** (N = 39)				**Improved *versus* Unimproved**	
	T1	**T2**			**T1**	**T2**			**T2**	
	Mean ± sd	*Mean ± sd*	***t*** *(df=110) (p)*	***d***	*Mean ± sd*	*Mean ± sd*	***t*** *(df=38) (p)*	***d***	***t*** *(df=148) (p)*	***d***
VSI	40.00 ± 8.71	21.05 ± 6.08	27.39 (<.001)	2.52	44.31 ± 5.55	48.23 ± 5.24	8.51 (<.001)	0.73	24.84 (<.001)	4.63
TAS-20 *	55.97 ± 12.22	51.49 ± 10.18	6.21 (<.001)	0.40	63.46 ± 7.35	63.92 ± 8.54	0.31 (.76)	0.06	6.83 (<.001)	1.27
DIF	20.68 ± 7.52	18.95 ± 5.82	2.99 (.003)	0.21	22.00 ± 6.93	23.77 ± 3.28	1.42 (.16)	0.33	4.90 (<.001)	0.91
DDF	13.78 ± 5.31	12.57 ± 5.41	2.05 (.04)	0.23	18.23 ± 4.07	18.62 ± 4.42	0.50 (.62)	0.09	6.28 (<.001)	1.17
EOT	21.51 ± 5.72	19.97 ± 4.67	2.55 (.01)	0.29	23.23 ± 5.88	21.54 ± 2.86	1.57 (.12)	0.37	1.96 (.05)	0.37
GSRS-IBS	3.41 ± 0.78	1.46 ± 0.34	26.37 (<.001)	3.24	3.52 ± 0.49	4.16 ± 0.62	9.19 (<.001)	1.14	33.51 (<.001)	6.28
Bloating	3.86 ± 1.07	1.48 ± 0.52	23.43 (<.001)	2.83	4.23 ± 0.60	4.85 ± 0.78	5.32 (<.001)	0.89	30.25 (<.001)	5.64
Diarrhea	3.26 ± 1.46	1.44 ± 0.47	15.63 (<.001)	1.68	3.36 ± 1.69	3.85 ± 1.86	5.28 (<.001)	0.28	12.53 (<.001)	2.35
Constipation	2.46 ± 1.59	1.32 ± 0.47	8.51 (<.001)	0.97	2.23 ± 1.38	3.00 ± 1.82	6.81 (<.001)	0.48	8.93 (<.001)	1.16
Pain	4.32 ± 0.80	1.78 ± 0.71	25.73 (<.001)	3.36	4.38 ± 0.63	5.11 ± 0.69	7.05 (<.001)	1.10	25.48 (<.001)	4.72

Satiety	3.13 ± 1.32	1.16 ± 0.37	16.12 (<.001)	2.03	3.53 ± 1.30	4.31 ± 1.34	4.52 (<.001)	0.59	22.51 (<.001)	4.20
HADS-A	6.95 ± 4.21	4.00 ± 2.92	14.68 (<.001)	0.81	6.77 ± 3.98	5.85 ± 3.44	3.38 (.002)	0.25	4.61 (<.001)	0.60
HADS-D	6.32 ± 3.88	3.51 ± 3.09	17.61 (<.001)	0.80	6.15 ± 4.01	6.38 ± 3.52	0.58 (.57)	0.06	4.81 (<.001)	0.89

***** Prevalence of alexithymia (TAS-20>60): At T1: improved group = 51 (45.9%), unimproved group = 33 (84.6%), between-group difference: χ^2=17.51, p<.001. At T2: improved group = 27 (24.3%), unimproved group = 32 (82%), between-group difference: χ^2=40.30, p<.001.

VSI = Visceral Sensitivity Index; *TAS-20* = Toronto Alexithymia Scale-20; *DIF* = Difficulty Identifying Feelings; *DDF* = Difficulty Describing Feelings; *EOT* = Externally Oriented Thinking; *GSRS-IBS* = Gastrointestinal Symptom Rating Scale-IBS; *HADS-A* = Hospital Anxiety and Depression Scale-Anxiety subscale; *HADS-D* = Hospital Anxiety and Depression Scale-Depression subscale.

Table 2. Hierarchical regression model predicting alexithymia (TAS-20) at T2 from baseline TAS-20 and T1 and T2 IBS symptoms (GSRS-IBS), GSA (VSI) and psychological distress (HADS) in the total sample.

Factors	R^2	ΔR^2	ΔF	p	df	B	semipartial *r*
Total sample							
TAS-20 (T1)	0.533		168.847	<.001	1,148	0.316	0.387
VSI (T1)	0.655	0.122	25.694	<.001	2,146	0.048	0.043
VSI (T2)						0.654	0.312
GSRS-IBS (T1)	0.685	0.031	7.021	.001	2,144	1.267	0.060
GSRS-IBS (T2)						-3.299	-0.161
HADS-A (T1)	0.698	0.013	1.520	.20	4,140	0.217	0.033
HADS-A (T2)						0.030	0.004
HADS-D (T1)						0.012	0.002
HADS-D (T2)						0.144	0.019

TAS-20 = Toronto Alexithymia Scale-20; *VSI* = Visceral Sensitivity Index; *GSRS-IBS* = Gastrointestinal Symptom Rating Scale-IBS; *HADS-A* = Hospital Anxiety and Depression Scale-Anxiety subscale; *HADS-D* = Hospital Anxiety and Depression Scale-Depression subscale; *T1* = baseline; *T2* = follow-up.

Table 3. Hierarchical regression model predicting GSA (VSI) at T2 from baseline VSI and T1 and T2 IBS symptoms (GSRS-IBS), alexithymia (TAS-20) and psychological distress (HADS) in the total sample.

Factors	R^2	ΔR^2	ΔF	p	df	B	semipartial *r*
VSI (T1)	0.118		11.329	.03	1,148	0.046	0.023
TAS-20 (T1)	0.476	0.358	35.923	<.001	2,146	0.109	0.152
TAS-20 (T2)						0.373	0.198
GSRS-IBS (T1)	0.863	0.386	202.527	<.001	2,144	1.502	0.060
GSRS-IBS (T2)						6.552	0.384
HADS-A (T1)	0.878	0.016	4.557	.002	4,140	0.858	0.116
HADS-A (T2)						0.330	0.038
HADS-D (T1)						0.713	0.077
HADS-D (T2)						0.348	0.038

TAS-20 = Toronto Alexithymia Scale-20; *VSI* = Visceral Sensitivity Index; *GSRS-IBS* = Gastrointestinal Symptom Rating Scale-IBS; *HADS-A* = Hospital Anxiety and Depression Scale-Anxiety subscale; *HADS-D* = Hospital Anxiety and Depression Scale-Depression subscale; *T1* = baseline; *T2* = follow-up.

Table 4. Individual variable logistic regression predicting treatment outcome.

						Final Model			
Variables	**Cox & Snell R^2**	**ΔR^2**	**χ^2**	**p**	**df**	**B**	**SE**	**Wald**	**p**
Age	0.007		1.143	.48	1	0.009	0.028	0.052	.83
GSRS-IBS	0.014	0.007	4.136	.009	1	0.263	0.103	6.501	.011
HADS-A	0.019	0.005	2.226	.14	1	0.187	0.105	2.059	.073
HADS-D	0.023	0.004	2.112	.15	1	0.133	0.107	1.537	.21
VSI	0.054	0.031	1.675	.21	1	0.010	0.037	0.074	.78
TAS-20	0.155	0.101	12.145	<.001	1	0.787	0.291	10.410	.001
DIF	0.143	0.089	9.354	<.001	1	0.684	0.243	8.194	.001
DDF	0.148	0.094	7.547	.001	1	0.714	0.294	9.994	.001
EOT	0.094	0.040	2.245	.08	1	0.198	0.097	3.154	.09

GSRS-IBS = Gastrointestinal Symptom Rating Scale-IBS; *HADS-A* = Hospital Anxiety and Depression Scale-Anxiety subscale; *HADS-D* = Hospital Anxiety and Depression Scale-Depression subscale; *VSI* = Visceral Sensitivity Index; *TAS-20* = Toronto Alexithymia Scale-20; *DIF* = Difficulty Identifying Feelings; *DDF* = Difficulty Describing Feelings; *EOT* = Externally Oriented Thinking.

Supplementary Table S1. Cross-correlations among scale scores at T1 and T2.

	IBS-SSS	VSI	TAS-20	DIF	DDF	EOT	GSRS-IBS	HADS-A	HADS-D
IBS-SSS	0.83 *	0.62 *	0.70 *	0.52 *	0.72 *	0.29 *	0.75 *	0.32 *	0.36 *
VSI	0.66 *	0.62 *	0.68 *	0.56 *	0.61 *	0.11	0.76 *	0.34 *	0.38 *
TAS-20	0.61 *	0.69 *	0.73 *	0.67 *	0.84 *	0.38 *	0.44 *	0.35 *	0.42 *
DIF	0.54 *	0.50 *	0.77 *	0.50 *	0.44 *	0.34 *	0.11	0.24 *	0.17
DDF	0.51 *	0.54 *	0.75 *	0.34 *	0.44 *	0.20	0.51 *	0.22 *	0.30 *
EOT	0.51 *	0.40 *	0.57 *	0.21 *	0.15	0.21	0.41 *	0.07	0.17
GSRS-IBS	0.47 *	0.40 *	0.51 *	0.33 *	0.41 *	0.41 *	0.17	0.32 *	0.37 *
HADS-A	0.08	0.09	0.28 *	0.24 *	0.22 *	0.28 *	0.03	0.76 *	0.78 *
HADS-D	0.21	0.26 *	0.33 *	0.27 *	0.27 *	0.38 *	0.21 *	0.80 *	0.81 *

Values above the diagonal represent correlations at T1, values below the diagonal at T2, and values in the diagonal (gray cells) between T1 and T2.

* $p < .01$

IBS-SSS = Irritable Bowel Syndrome Severity Scoring System; *VSI* = Visceral Sensitivity Index; *TAS-20* = Toronto Alexithymia Scale-20; *DIF* = Difficulty Identifying Feelings; *DDF* = Difficulty Describing Feelings; *EOT* = Externally Oriented Thinking; *GSRS-IBS* = Gastrointestinal Symptom Rating Scale-IBS; *HADS-A* = Hospital Anxiety and Depression Scale-Anxiety subscale; *HADS-D* = Hospital Anxiety and Depression Scale-Depression subscale.

Supplementary Table S2. Hierarchical regression models predicting alexithymia (TAS-20) at T2 from baseline TAS-20 and T1 and T2 IBS symptoms (GSRS-IBS), GSA (VSI) and psychological distress (HADS) in the improved and unimproved groups.

Factors	R^2	R^2 change	F change	p	df	B	semipartial *r*
Improved group							
TAS-20 (T1)	0.614		173.672	<.001	1,109	0.473	0.305
VSI (T1)	0.651	0.037	5.626	.005	2,107	-0.020	-0.012
VSI (T2)						0.411	0.165
GSRS-IBS (T1)	0.680	0.029	4.818	.01	2,105	0.854	0.046
GSRS-IBS (T2)						-0.591	-0.172
HADS-A (T1)	0.692	0.012	0.990	.42	4,101	-0.031	-0.005
HADS-A (T2)						0.229	0.027
HADS-D (T1)						-0.047	-0.005
HADS-D (T2)						0.221	0.025
Unimproved group							
TAS-20 (T1)	0.481		13.172	<.001	1,37	2.164	0.453
VSI (T1)	0.570	0.090	3.647	.008	2,35	0.071	0.032
VSI (T2)						0.409	0.285
GSRS-IBS (T1)	0.620	0.050	1.746	.19	2,33	0.117	0.042
GSRS-IBS (T2)						0.219	0.032
HADS-A (T1)	0.652	0.032	0.884	.12	4,29	0.068	0.044
HADS-A (T2)						0.104	0.106
HADS-D (T1)						0.092	0.060
HADS-D (T2)						0.112	0.112

TAS-20 = Toronto Alexithymia Scale-20; *VSI* = Visceral Sensitivity Index; *GSRS-IBS* = Gastrointestinal Symptom Rating Scale-IBS; *HADS-A* = Hospital Anxiety and Depression Scale-Anxiety subscale; *HADS-D* = Hospital Anxiety and Depression Scale-Depression subscale; *T1* = baseline; *T2* = follow-up.

Supplementary Table S3. Hierarchical regression models predicting GSA (VSI) at T2 from baseline VSI and T1 and T2 IBS symptoms (GSRS-IBS), alexithymia (TAS-20) and psychological distress (HADS) in the two outcome-related samples.

Factors	R^2	ΔR^2	ΔF	p	df	B	semipartial *r*
Improved group							
VSI (T1)	0.112		10.903	.03	1,109	0.078	0.076
TAS-20 (T1)	0.568	0.456	30.971	<.001	2,107	0.196	0.194
TAS-20 (T2)						0.198	0.192
GSRS-IBS (T1)	0.570	0.002	0.258	.77	2,105	0.039	0.004
GSRS-IBS (T2)						0.285	0.014
HADS-A (T1)	0.585	0.015	0.890	.47	4,101	0.374	0.102
HADS-A (T2)						0.361	0.072
HADS-D (T1)						0.164	0.031
HADS-D (T2)						0.206	0.039
Unimproved group							
VSI (T1)	0.232		2.579	.02	1,37	0.154	0.112
TAS-20 (T1)	0.766	0.534	4.015	.03	2,35	0.009	0.186
TAS-20 (T2)						0.454	0.282
GSRS-IBS (T1)	0.812	0.046	4.015	.02	2,33	0.320	0.183
GSRS-IBS (T2)						0.400	0.272
HADS-A (T1)	0.928	0.116	11.656	<.001	4,29	0.612	0.070
HADS-A (T2)						0.392	0.211
HADS-D (T1)						0.711	0.122
HADS-D (T2)						0.728	0.197

VSI = Visceral Sensitivity Index; *TAS-20* = Toronto Alexithymia Scale-20; *GSRS-IBS* = Gastrointestinal Symptom Rating Scale-IBS; *HADS-A* = Hospital Anxiety and Depression Scale-Anxiety subscale; *HADS-D* = Hospital Anxiety and Depression Scale-Depression subscale; *T1* = baseline; *T2* = follow-up.

Supplementary Table S4. Hierarchical regression predicting proportion of change in IBS-SSS scores.

Variables	R^2	ΔR^2	F	p	df	B	semipartial *r*
Age	0.007		0.051	.63	1,148	-0.031	-0.093
GSRS-IBS	0.020	0.013	3.086	.08	1,147	5.073	-0.109
HADS-A	0.023	0.003	0.413	.52	1,146	-1.785	-0.148
HADS-D	0.024	0.000	0.055	.81	1,145	-0.524	-0.042
VSI	0.056	0.032	2.518	.21	1,144	-0.398	-0.084
TAS-20	0.230	0.174	30.809	<.001	1,143	-1.463	-0.406
DIF	0.222	0.166	26.434	<.001	1,143	1.562	-0.398
DDF	0.192	0.134	21.868	<.001	1,143	1.448	-0.356
EOT	0.085	0.029	1.132	.11	1,143	0.229	-0.138

GSRS-IBS = Gastrointestinal Symptom Rating Scale-IBS; *HADS-A* = Hospital Anxiety and Depression Scale-Anxiety subscale; *HADS-D* = Hospital Anxiety and Depression Scale-Depression subscale; *VSI* = Visceral Sensitivity Index; *TAS-20* = Toronto Alexithymia Scale-20; *DIF* = Difficulty Identifying Feelings; *DDF* = Difficulty Describing Feelings; *EOT* = Externally Oriented Thinking.