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Stress Reactivity in Traditional Chinese Medicine–Based Subgroups of Patients with Irritable Bowel Syndrome

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Abstract

Objectives: This study aimed to examine differences in autonomic responses to stress, pain perception, and the role of negative affect in these responses in individuals with irritable bowel syndrome (IBS) according to Traditional Chinese Medicine (TCM) classifications.
Design: Fifty-nine female patients with IBS age 18–65 years diagnosed by TCM practitioners as showing primarily an excess ($n = 32$) or an overlap ($n = 27$) pattern (mixed excess and deficiency) were assessed for symptom differences, heart rate, and skin conductance responses to a psychosocial stressor and pain perception.
Settings/Locations: University of California in Los Angeles, California.
Results: Compared with the excess group, the overlap group showed significantly greater overall gastrointestinal symptom severity, abdominal pain, and negative affect. The excess group with higher levels of negative affect showed greater reactivity to stress, whereas the overlap group showed an opposite response pattern. The overlap group showed increased cold sensitivity.
Conclusions: IBS patients with the overlap pattern have greater disease severity and comorbidity than those with excess alone. Those with excess showed a pattern of increased stress response with greater negative affect, whereas the overlap group with greater deficiency showed lower physiologic arousal with greater negative affect, consistent with depletion resulting from allostatic load.

Introduction

Irritable bowel syndrome (IBS) is a chronic gastrointestinal (GI) disorder affecting 7%–20% of the U.S. population.[1] It is characterized by recurrent abdominal pain or discomfort associated with bowel function alternation (diarrhea and/or constipation).[2] Therapy for IBS, including pharmacologic and diet interventions, has had limited success despite the availability of several medications that acutely alter bowel habits.[3] Several promising new avenues for IBS treatment, including use of probiotics, antibiotics, and centrally acting medications, may help subsets of patients, but further research is needed.[4,5] Patients with IBS frequently report a variety of non-GI symptoms, such as fatigue, menstrual problems, sexual dysfunction, and emotional disturbance.[6] IBS is also associated with high comorbidity with anxiety and depression; this has led to a conceptualization of IBS, as well as other functional GI disorders, as partly the result of centrally mediated changes in brain–gut communication.[7]

Given the lack of effective treatments, 30%–50% of patients with IBS seek complementary and alternative medicine treatments, and many consider them beneficial.[8,9] These include herbal and acupuncture treatments based on Traditional Chinese Medicine (TCM),[10,11] as well as yoga, meditation, and other mind–body interventions.[12] Small clinical trials suggest these treatments may be beneficial, but it is not clear how well they will fare in larger and better-controlled trials.[13–17]

It is well recognized that the accepted Rome III diagnostic criteria for IBS identify a heterogeneous group of patients in terms of potential pathophysiology.[18] However, IBS subgrouping schema beyond predominant bowel habits have not been particularly successful in identifying patients who will respond differently to various therapies. We have

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previously suggested that TCM offers a possible alternative to Western medicine subgrouping approaches to IBS.[11] In TCM, patients with IBS are seen as a heterogeneous population with fundamentally different underlying pathophysiologic disturbances. Patients are classified into individual patterns of dysregulation based on an overall state of health reflected by a constellation of both intestinal and extraintestinal symptoms. Most importantly, specific therapies are tailored to these individual subtypes.[19–21] Although many TCM patterns are seen in patients with IBS, it is most common to separate patients according to patterns of "excess" (liver *qi* stagnation), "deficiency" (spleen *qi* deficiency), or "overlap" (mixture of excess and deficiency).[11]

Conceptually, the excess and deficiency patterns form a clinical continuum from acute to chronic and "overactive" to "depleted," respectively, with the overlap pattern in between. In TCM, the excess pattern is particularly seen following acute to subacute physical and psychological stressors and is commonly associated with emotional feelings of anger and frustration. In contrast, the deficiency pattern is observed in association with chronic illness, persistent strenuous life events, and prolonged exposures to adverse environmental factors, such as cold.[19,20] Exhaustive lifestyle factors, such as overwork, long-term engagement in mentally taxing activities, and poor rest and sleep are further contributing stressors. Characteristics of the deficiency group reflect a loss of general resilience due to prolonged strain on an individual, which is seen in such symptoms as fatigue, increased susceptibility to infections, compromised pain tolerance, and intolerance to cold exposure.[19] It is commonly associated with emotional feelings of worry and anxiety.[19,20]

Tan and colleagues used intestinal and extraintestinal symptoms (bowel-predominant and psychological-predominant) to provide operational criteria supporting the existence of TCM-based subgroups in IBS.[11] However, there has been little empirical study of how different TCM patterns may be related to underlying pathophysiology in a condition such as IBS or how TCM patterns may be associated with physiologic responses to stress. To examine differences in psychological and physiologic processes related to TCM subgroups of patients with IBS, the aims of the current exploratory were to (1) determine the reliability of classification of patients with IBS into TCM-based subgroups based on assessment by TCM practitioners; (2) determine the frequency of relatively pure excess and deficiency as well as overlap patterns in the female IBS population; (3) determine whether patients with IBS showing relatively greater excess or deficiency characteristics differ in IBS and extraintestinal symptoms; (4) determine whether patients with IBS showing relatively greater excess or deficiency differ in physiologic responses to stress and cutaneous heat and cold consistent with TCM theory; and (5) examine the role of IBS severity and negative affect as moderators of physiologic differences between TCM classifications.

Materials and Methods

Patients

Fifty-nine women age 18–65 years with IBS based on Rome III criteria[22] and symptoms lasting a minimum of 6 months were recruited by community advertisement. IBS diagnosis and inclusion/exclusion status were determined during a physical examination by a physician or nurse practitioner experienced in functional GI disorders. Patients were excluded if they had been involved in a TCM-based treatment 3 weeks before study screening, had undergone GI surgery, had an active organic GI disorder, had a severe psychiatric disorder, used warfarin or other blood-thinning drugs, were pregnant, or were using pain medications or β-blockers.

All patients were evaluated independently by two experienced California state–licensed TCM practitioners at Emperor's College in Santa Monica, California. The practitioners used TCM paradigm–based history and physical examination, including tongue and pulse assessment, to assign each patient to one of three distinct predominant TCM patterns: excess, deficiency, or overlap (relatively equal symptoms of both patterns). Although there was not a standardized set of history questions to allow the practitioners to use their own procedures, both typically asked about mood, menstrual cycle, activities, physical symptoms, and sensitivities. Practitioners were blind to the results of the study questionnaires and laboratory tests. Patients were included in the physiologic portion of the study only if both practitioners agreed on the TCM diagnosis. Because no pure deficiency cases were found among the 72 patients evaluated in this study, the analysis of laboratory data examined the patients with pure excess compared with those with an overlap diagnosis.

The University of California, Los Angeles, Institutional Review Board approved this study. All patients provided signed informed consent.

Symptoms and psychological instruments

Patients answered self-report questions on age, ethnicity, IBS chronicity (in years), overall severity of GI symptoms during the past week (on a 0- to 20-point numeric rating scale anchored by "none" and "most intense symptoms imaginable"), and a similar 20-point numeric rating scale for severity of abdominal pain during the past week. They also completed the Hospital Anxiety and Depression Scale (HADS), a 14-item self-report measure of current anxiety and depression symptoms validated for nonpsychiatric samples.[23] Total HADS score was used as a general measure of negative affect.

Psychophysiological measures

Continuous measures of heart rate and skin conductance level (SCL) were recorded throughout the laboratory session and processed by using Biopac MP100 hardware and AcqKnowledge 3.8.2 software (Biopac, Goleta, California). For heart rate, the electrocardiogram was recorded by using electrocardiography electrodes applied to the right shoulder below the clavicle and to the left leg above the ankle. For SCL, two Ag/AgCl 1-cm-diameter electrodes were attached to the distal phalanges of the ring and little finger on the palmar side of the patient's nondominant hand. For each period, mean heart rate was based on the average heart period, and mean SCL was the mean of all SCL values. SCL data were log-transformed to normalize the distribution.

Laboratory procedures

The protocol began with a 10-minute resting baseline during which the patients were comfortably seated in a chair

and instructed to minimize movement and to rest. The patients were monitored via video camera. Baseline was followed by three tasks: the Trier Social Stress Test (TSST) task, pain sensitivity assessment using a pressure algometer, and thermal pain sensitivity using a computer controlled thermal stimulator. The tasks were presented in three different orders counterbalanced across patients.

TSST task

The TSST task is a social and cognitive stressor consisting of three 5-minute periods: preparation of speech, speech, and mental arithmetic, in that order. Patients were asked to talk about their personal strengths and weaknesses, interpersonal relationships, professional capabilities, priorities, and values. They were informed that the speech would be videotaped and rated later by evaluators on the basis of their style, nonverbal behavior, poise, and overall quality of the presentation. After instruction, patients were given 5 minutes to prepare the speech. During the speech, at least 5 negative feedback statements were provided by an examiner present in the room with the patient (e.g., "You are being superficial"). In the mental arithmetic task, patients were asked to successively subtract by 13, starting from 1022. If the patient made an error, she was asked to begin again from 1022. If a patient appeared unable to continue, she was asked to start over and subtract by 7.

Temperature (heat and cold) pain sensitivity task

Temperature sensitivity was assessed with a thermal stimulator (TSA-II, Medoc Ltd., Ramat Yishai, Israel) with a 25×50 mm Peltier contact thermode applied to the palmer side of the right forearm. The heat stimulations increased at the rate of 1.5°/sec from 32°C to 50°C, whereas the cold stimulations decreased at the same rate from 32°C to 0°C. The patients indicated "stop" when they could not tolerate the temperature, which was recorded as their heat or cold tolerance. Each heat and cold test was repeated five times, with 30 seconds of rest between each test.

Data analysis

Reliability of the TCM subgrouping was determined by diagnostic agreement between two experienced and certified TCM practitioners. The two TCM subgroups were then compared on demographic characteristics; symptom severity; psychological measures; and baseline heart rate, SCL, and heat and cold tolerance using chi-square tests for categorical variables and *t*-tests for continuous variables. Heart rate and SCL during baseline and the TSST were analyzed by using a mixed-model statistical approach (Proc Mixed, version 9.2; SAS Institute, Cary, North Carolina). Mixed-model analysis of repeated measurements is a recommended approach for continuous psychophysiologic data.[24] The first analysis examined whether the two diagnostic groups (excess, overlap) differed significantly across four periods (initial baseline, preparation of speech, speech, mental arithmetic), with an adjustment for task order. The role of IBS severity and negative affect was then examined by adding each potential moderator one at a time as a factor in the model, which became a three-way model (groups × periods × moderator [IBS severity or HADS score]). The models were all adjusted for task order. Post hoc comparisons between the two groups were carried out by using Bonferroni adjustments for multiple comparisons: (1) to compare the two subgroups at each period and (2) to compare the two subgroups in the change from baseline to each stress period for differing levels of IBS severity and negative affect (HADS).

A similar statistical procedure as above was applied for the heat and cold tasks. A three-way model (groups × trials × moderator [IBS severity or HADS]) with an adjustment for task order examined the differences between the two groups for different levels of moderators. Note that although all analyses treat the moderators as continuous measures, for display purposes the figures plot the values for each group at three standard levels of the moderator variable (mean and mean ± 1 standard deviation [SD]). Significance level was set at $p < 0.05$ in all analyses.

Results

TCM diagnostic agreement

Of the 72 patients evaluated independently by the two experienced TCM practitioners, none were given a diagnosis of deficiency by both practitioners. Overall, agreement between the two independent raters was at 82% (excellent reliability).[25] The 13 patients for whom the TCM practitioners did not agree on a pattern diagnosis were excluded from the laboratory analysis, leaving 59 patients (32 in the excess group and 27 in the overlap group) for the analyses reported below.

Baseline

Table 1 shows the demographic and medical characteristics of the patients. No differences were found between the two subgroups in age, education, ethnicity, body–mass index, and bowel habit and years diagnosed with IBS. The overlap group, however, compared with the excess group, had higher scores on negative affect (total HADS, [$t(57) = (2.50; p = 0.02]$),

Table 1. Demographic Characteristics of the Excess and Overlap Groups of Female Patients with Irritable Bowel Syndrome

Characteristic	*Excess group (n = 32)*	*Overlap group (n = 27)*	p-*Value*
Age (yr)	33.5 ± 12.2	38 ± 12.7	0.20
Body–mass index (kg/m^2)	22.3 ± 3.9	24.9 ± 5.8	0.06
IBS chronicity and severity			
Bowel habit			0.40
Constipation	37.5 (12)	22.2 (6)	
Diarrhea	25.0 (8)	25.9 (7)	
Alternate/mixed/ unspecified	37.5 (12)	51.9 (14)	
Years Diagnosed with IBS	12.5 ± 10.4	15.0 ± 11.6	0.41
Overall GI symptoms	10.3 ± 4.1	12.2 ± 2.9	0.04
Abdominal pain	9.3 ± 4.3	11.5 ± 3.8	0.04
HADS total score	10.4 ± 6.8	15.1 ± 7.6	0.02

Values are expressed as the percentage (number) of patients or the mean ± standard deviation.

GI, gastrointestinal; HADS, Hospital Anxiety and Depression Scale; IBS, irritable bowel syndrome.

overall GI symptom severity ($t(55)(2.02$; $p = 0.04$), and abdominal pain ($t(57) = (2.04$; $p = 0.04$). Although the difference between the groups in BMI was not significant, the overlap has a higher BMI than the excess group. For psychophysiologic measures, the two groups did not differ significantly on baseline measures of heart rate and SCL (not shown in Table 1).

TSST

The group × period analysis indicated a significant effect for period ($F(3, 165) = 41.70$; $p < 0.01$) but no main effect or interaction with the TCM group. As shown in Table 2, heart rate increased from the baseline, peaked during the speech portion of the test, and then declined during the mental arithmetic period. SCL showed a similar pattern, although it did not decline during mental arithmetic.

IBS severity

When IBS severity was added as a moderator in the heart rate and SC analyses, no significant main effects or interactions with TCM group were found.

Negative affect (HADS)

The group × period × HADS model revealed a significant three-way interaction ($F(3, 159) = 4.36$; $p < 0.01$) for heart rate. Figure 1 illustrates this interaction by showing the estimated heart rate response for the two groups at three levels of HADS score: the mean, 1 SD above the mean, and 1 SD below the mean. As seen in Figure 1, there was a greater heart rate response to stress at higher levels of HADS score in the excess group, whereas the overlap group showed the opposite pattern (greater heart rate response with lower total scores). This pattern was confirmed in the *post hoc* contrasts. The two groups did not differ in heart rate at baseline across HADS score levels. However, they differed significantly in terms of changes in heart rate across HADS score levels during speech preparation ($F(2, 159) = 3.06$; $p = 0.05$) and speech ($F(2, 159) = 4.74$; $p = .01$). For both tasks, the excess group showed significantly higher heart rate at the higher negative affect level, while the overlap group showed lower heart rate with higher negative affect. No significant group differences were found for the math task in this analysis.

The changes from the baseline to speech period ($F(2, 159) = 3.41$; $p = 0.04$) as well as from the baseline to preparation of speech ($F(2, 159) = 5.14$; $p < 0.01$) were also significantly different between groups based on HADS score. The excess group showed an increase in heart rate response with increasing HADS score, and the overlap group showed the opposite pattern (greater heart rate response with lower negative affect). However, the change from the baseline to math period was not significant.

When the HADS score was included in the SCL model (Fig. 1, bottom panel), there were no significant effects involving TCM group. However, the post hoc comparisons showed significant differences from baseline to the speech period ($F(2, 151) = 5.47$; $p < 0.01$) and from baseline to preparation of speech ($F(2, 151)$ 3.12; $p < 0.05$).

Table 2. Heart Rate and Skin Conductance Levels During the Trier Social Stress Test

Trier Social Stress Test	*Heart rate (beats/min)*	*SCL (μsec)*
Baseline	71.4 ± 10.2	1.07 ± 0.6
Preparation of speech	76.1 ± 10.5*	1.68 ± 0.6*
Speech	81.4 ± 12.2*	1.89 ± 0.6*
Mental arithmetic	76.4 ± 10.2*	1.89 ± 0.6*

*Different from baseline at $p < 0.05$.
SCL, skin conductance level.

Temperature sensitivity (heat and cold tolerance) test

The TCM groups did not differ in heat tolerance. In addition, no significant main effects or interactions with TCM group were found in the analysis of heat tolerance when negative affect (HADS) or IBS severity was included as moderators in the analysis.

Cold tolerance did not differ significantly between the TCM groups in the analysis without moderators, and there were no significant main effects or interactions with TCM group in the analysis that included IBS severity as a moderator. However, when the HADS score was included in the model examining cold tolerance, there was a significant main effect for TCM group ($F(1, 207) = 6.77$; $p < 0.01$) and a significant two-way interaction (group × HADS score; $F(1, 207) = 3.93$; $p = 0.04$). As shown in Figure 2, overall the excess group had a higher cold tolerance. In addition, cold tolerance in the excess group slightly decreased as HADS score increased, whereas in the overlap group, cold tolerance increased as HADS score increased. The post hoc comparisons showed a significant main effect only at the low level ((1 SD) of anxiety ($F(1, 207) = (2.65$; $p < 0.01$).

Discussion

The current study is believed to be the first to directly test whether patients with IBS, subgrouped by TCM practitioners, show physiologic and symptom differences in accordance with TCM pattern diagnosis theory. The first finding of interest was that the subgrouping determination made independently by the TCM practitioners was generally reliable. The 82% agreement is similar to what is found for TCM and Western diagnosis of IBS.[26,27] Another important finding was that the pure deficiency pattern was rare in this sample. This is somewhat surprising because a deficiency pattern has been considered in TCM as an important component of chronic illnesses, including IBS. It is possible that those with a pure deficiency pattern self-selected out of volunteering for a research study. The deficiency pattern is associated with high levels of fatigue and lethargy in addition to an increase in symptoms with even minimal activity, and these characteristics may have led to reluctance to participate. An informal review of patient charts seen in the TCM clinic for any chronic pain problem also revealed a general lack of pure deficiency diagnoses, so it is likely that the absence of deficiency patients in the clinic is not unique to IBS. The age of the patients may also have played a role as pure deficiency occurs more frequently at older ages.

The comparison of the two patterns that were included in the study clearly indicated that those with overlap (and therefore higher amounts of deficiency) had greater IBS severity and comorbidity than those with excess alone. In

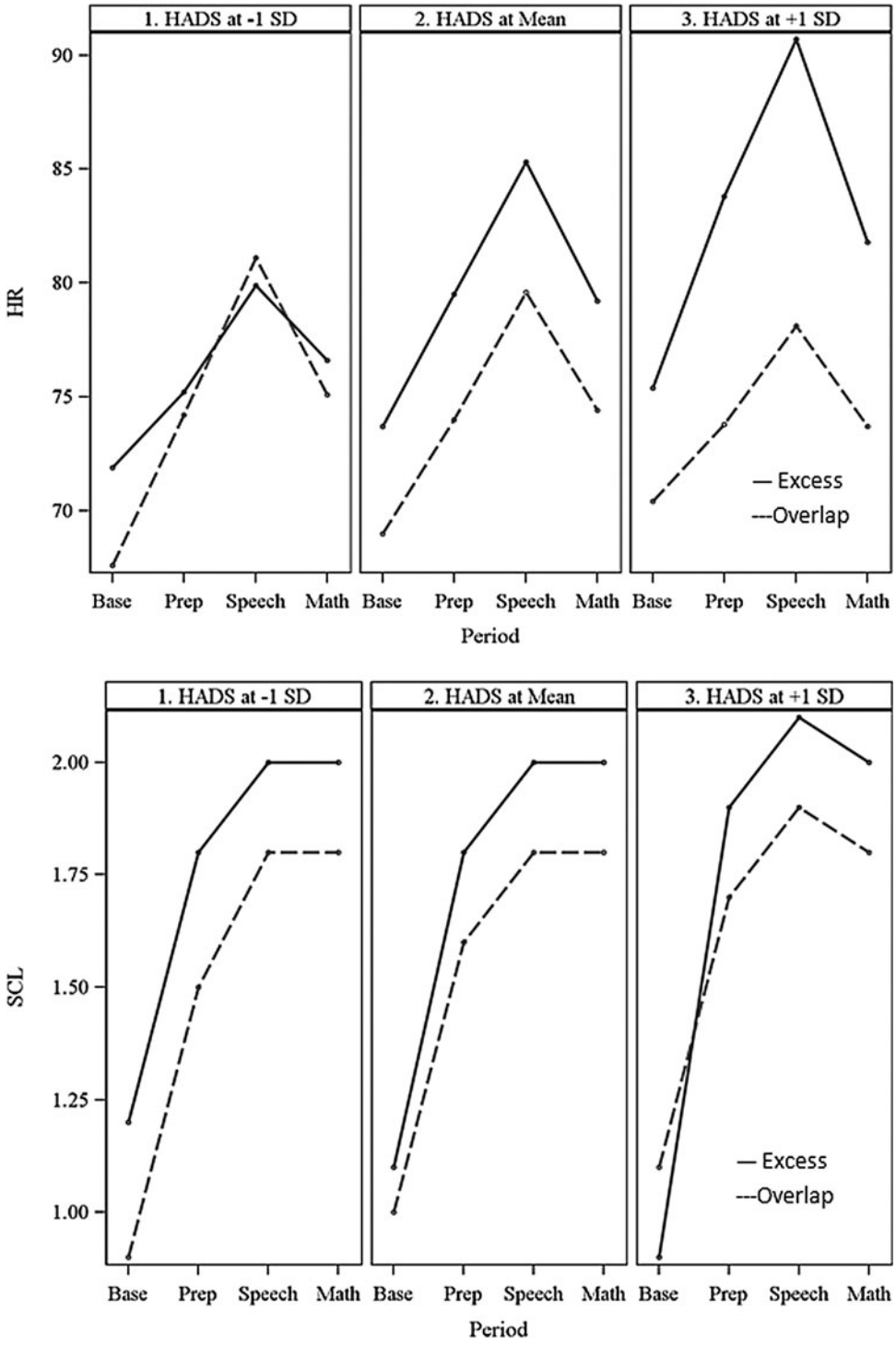

FIG. 1. Heart rate (HR) and skin conductance level (SCL) responses for the excess and overlap groups as a function of Hospital Anxiety and Depression Scale (HADS) scores. Estimated mean heart rate (top panel) and SCL (bottom panel) for excess and overlap groups at the mean and ± 1 standard deviation (SD) of the mean on HADS. Base, baseline; prep, preparation of speech task; math, mental arithmetic task.

addition, although the two TCM groups *per se* did not differ in their autonomic response to the TSST, they did differ as a function of individual levels of negative affect. At least for heart rate, those with excess showed a pattern of increased autonomic arousal to the stressor in the presence of greater negative affect, whereas those with overlap showed an opposite pattern: lower arousal to the psychological stressor with greater negative affect. The overlap group also had a lower cold tolerance than the excess group when controlling for negative affect.

It is important to note that the TCM diagnosis added unique variance in determining the stress response because neither negative affect nor IBS severity alone was related to autonomic reactivity or pain tolerance.

Symptom differences between TCM patterns

The two TCM groups did not differ in terms of predominant bowel habit or chronicity of IBS symptoms. However, the overlap group did have somewhat higher levels of IBS

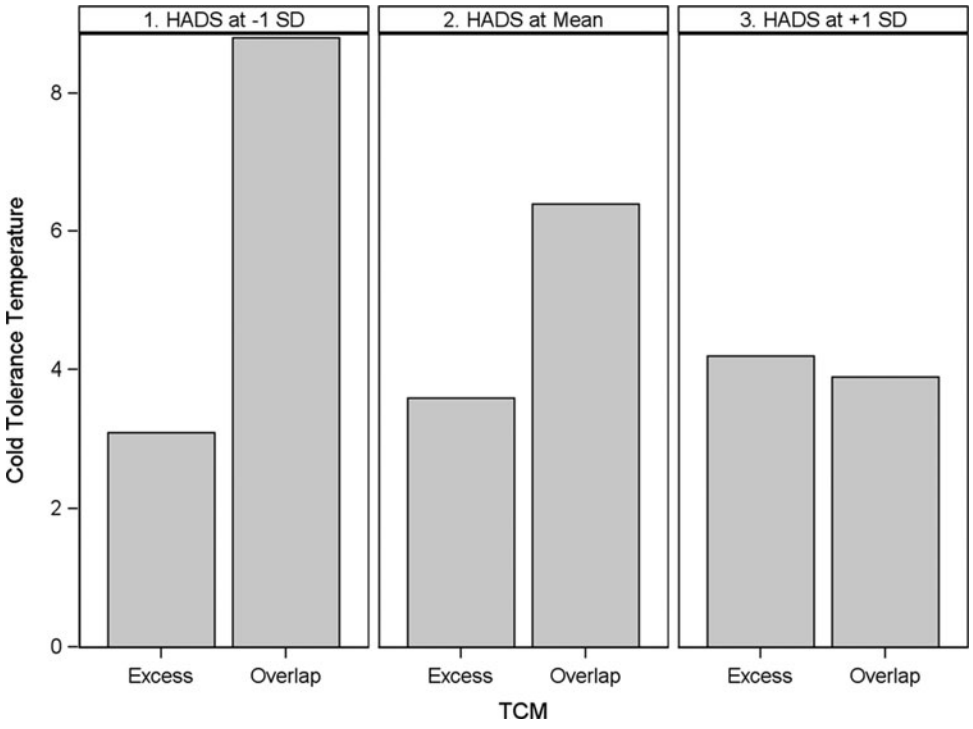

FIG. 2. Cold tolerance for the excess and overlap groups. Estimated cold tolerance for excess and overlap groups at the mean and ±1 standard deviation (SD) of the mean on the Hospital Anxiety and Depression Scale (HADS). TCM, Traditional Chinese Medicine.

symptom severity and abdominal pain. The increased levels of negative affect for the overlap group suggests this TCM pattern is associated with increased symptoms of anxiety and depression and poorer health-related quality of life. Although this study did not examine specific psychological or somatic symptoms (e.g. fatigue, anxiety, worry), patients with an overlap pattern, and therefore increased characteristics of deficiency, are hypothesized to experience greater fatigue, increase in symptoms with activity, and perhaps depression compared with those with an excess pattern.[28] These characteristics may correspond with the greater reports of IBS and mood symptoms found for this group. The lack of TCM group differences in predominant bowel habit and chronicity of IBS is consistent with the TCM diagnoses being in large part independent of the most common IBS subgrouping categories.

TCM pattern diagnoses and allostatic load

Allostasis refers to the process by which our bodies maintain homeostasis in response to environmental change or stressors.[29] Key homeostatic mechanisms involved in allostasis include ascending monoaminergic systems, the hypothalamic-pituitary-adrenal axis, endogenous pain modulation networks, and autonomic and skeletomotor pathways. Allostatic responses to limited or acute changes in the environment are generally adaptive; however, with persistent stressors and/or lowered resilience in the system, even lesser stressors may result in maladaptive responses, reflected by sustained hyperactivity or ineffectiveness of allostatic mediators. This breakdown of the system and the consequent inability of the organism to maintain homeostasis ultimately result in illness and system failure.[28] The damage that occurs within the organism when the allostatic response functions improperly is referred to as allostatic load. Allostatic load is associated with many common medical syndromes, ranging from heart disease to chronic pain syndromes.[28,30,31] The relationship between stress and the homeostatic response has been described as an inverted U function. Up to a point, increasing stress or demand is associated with increased arousal as part of the adaptive response. However, with very high or sustained levels of stress or in the presence of high allostatic load, increasing demand is met with reduced responding due to depletion and system breakdown.

We have previously hypothesized that TCM diagnostic patterns of excess and deficiency may in part mirror this system and reflect both the general state of homeostatic regulation and propensities to respond to stress with greater or lesser reserve.[28] We hypothesized that those with an excess pattern would show heightened arousal during stress and that greater deficiency would be associated with allostatic load and depletion. In the present study, the overlap group with greater deficiency did show increased symptoms and increased comorbidity, consistent with increased allostatic load. The groups did not differ on overall stress response; however, if one considers negative affect as a marker of chronic stress, then the more deficient patients did show evidence of greater allostatic load in terms of smaller stress responses at higher levels of negative affect instead of greater stress responses (as in the excess group). In other words, the peak of the inverted U or the tipping point where depleted-type stress responses begin to occur may be shifted to the left in the overlap patients. The finding of decreased cold (but not heat) tolerance in the overlap group is consistent with the tenant of TCM theory that greater deficiency is associated with a loss of resilience and tolerance to physiologic stressors, particularly those such as cold exposure, which TCM deems more energy depleting.[11,20] The neurobiological underpinnings of the major TCM patterns are not well

understood. Recent findings from brain imaging studies indicate continuous and specific central modulation of peripheral biology, including the GI tract, pain sensitivity, and immune function, all processes which affect IBS symptoms.[32] In addition, input from the major organ systems is clearly well represented in the brain, and this ascending input probably has a significant influence on higher brain processes involving attention, affect, and cognition. It is therefore possible that the TCM patterns may reflect specific states of homeostatic regulation that arise in the context of chronic stress.[28]

Limitations of the study

Although the current study provides novel data regarding TCM subgroups, it is limited by having only two TCM patterns represented. As practiced clinically, TCM incorporates many more specific patterns and methods of classification, and patients can be diagnosed with more than one. While excess and deficiency are arguably the two most common patterns for a chronic illness population, further study of other patterns is warranted; however, it may be especially difficult given the complexity and heterogeneous nature of the various TCM systems. In addition, it is likely that the major results are not unique to IBS, and further study of other chronic pain or illness groups are needed to test this hypothesis. The current study also did not examine the relationship between specific characteristics thought to be associated with each TCM pattern (e.g., fatigue and worry with deficiency; anger with excess) and the physiologic responses, and this may be also be a fruitful area for future study. Despite these limitations, the results strongly support the original hypothesis that there are important subgroups of patients with IBS distinguishable by extraintestinal symptoms and altered stress responses that may well require different treatments. These data may help explain why TCM (e.g., acupuncture) and Western treatments for IBS have very high failure rates when applied to all diagnosed patients and point toward increased attention to various new ways to subgroup patients for specific treatments.

Conclusions

This study has shown that two major TCM subgroups can be identified within the IBS population and that these two groups have differing autonomic responses to psychological stress and tolerance to cold stimuli that are not dependent on IBS severity, predominant bowel habit, or chronicity.

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Author Disclosure Statement

No competing financial interests exist.

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