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RESEARCH ARTICLE

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Cognitive function in patients with irritable bowel syndrome: impairment is common and only weakly correlated with depression/anxiety and severity of gastrointestinal symptoms

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ABSTRACT

Objective: To investigate cognitive function in patients with irritable bowel syndrome (IBS) and its relation to anxiety/depression and severity of gastrointestinal (GI) symptoms.

Methods: Patients with IBS ($n=65$) and healthy controls (HCs, $n=37$) performed the ten subtests of the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS). Age-normed index scores of five cognitive domains (Immediate memory, Visuospatial function, Language function, Attention, Recall) and a total (Fullscale) score were derived from the performance. Emotional function was assessed using the Hospital Anxiety and Depression Scale (HADS), and the IBS Symptom Scoring System (IBS-SSS) was used to define the severity of GI symptoms.

Results: Patients with IBS reported significantly higher scores than the HC group on symptom measures of anxiety and depression, and significantly lower scores on the Immediate memory, Recall, and Fullscale RBANS indexes. Approximately 30% of the IBS patients obtained index scores at least one standard deviation below the population mean, and more than 50% scored above the screening threshold for an anxiety disorder. The severity of GI symptoms was significantly correlated with the severity level of anxiety symptoms ($p=.006$), but neither the severity level of emotional nor GI symptoms was significantly correlated with the RBANS index scores in the IBS group.

Conclusion: Cognitive and emotional function were more severely affected in patients with IBS than in HCs. The weak correlation between the two functional areas suggests that both should be assessed as part of a clinical examination of patients with IBS.

PRACTITIONERS' POINTS

- Cognitive and emotional function should be assessed in patients with IBS.
- Cognitive impairment was less closely related to symptoms of anxiety/depression and severity of GI symptoms than expected.
- An independent contribution of both emotional symptoms and cognitive function should be considered when developing treatment programs for patients with IBS.

Abbreviations: RBANS: Repeatable Battery for the Assessment of Neuropsychological Status; HADS: Hospital Anxiety and Depression Scale; IBS: Irritable Bowel Syndrome; IBS-SSS: Irritable Bowel Syndrome Severity Scoring System.

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Introduction

Irritable Bowel Syndrome (IBS) is a prevalent disorder, reported to affect one in ten people globally [1]. The disorder is characterized by a high frequency of recurrent abdominal pain and changes in bowel habits over time in the absence of a known detectable organic cause [2]. Historically, symptoms outside the gastrointestinal (GI) system have been described as secondary or comorbid to gastrointestinal (GI) symptoms, and the diagnosis is still primarily based on the

gut-restricted Rome-IV criteria [3]. However, there has been a growing awareness within the field to broaden the definition of clinical symptoms associated with IBS. This shift suggests that emotional problems should be considered when assessing and selecting treatment approaches for patients with IBS [4]. Indeed, 30 – 40% of IBS patients fulfill the diagnostic criteria of anxiety and/or depression, respectively [5,6]. Some of these patients are shown to respond better to psychological treatment than to interventions aimed directly at alleviating

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the GI symptoms [7]. A recent study further supported a close co-existence between emotional and GI symptoms by showing that anxiety and IBS share a genetic vulnerability that affects both the enteric and central nervous system, causing gut-brain disturbances in IBS [8].

Several studies have confirmed the importance of the rich communication between the gut and the brain in patients with IBS [9–12] and other diseases defined as disorders of the gut-brain interaction (DGBI). In a bidirectional pathway between the gut and the brain, the gut microbiota and its interaction with the enteric nervous system, the enteroendocrine system, and the gut-associated immune system are suggested to affect brain structure [13,14] and function [12,15], and vice versa. This so-called gut-brain axis has fueled an interest in investigating cognitive impairment in patients with IBS and other DGBIs [4,16]. Assumptions about cognitive impairment in patients with IBS are indicated by studies including brain imaging data and measures of gut microbiota. Brain imaging studies comparing IBS patients with healthy controls have shown smaller volumes in brain regions associated with stress [17], visceral stimulation [18], sensory integration [19,20], affective processing [21], somatic pain [11] as well as cognitive/executive functions [22]. Other studies have shown that alterations in gut microbiota affect cognitive performance in both human and animal models [23–25]. Further, so-called “brain fog”, characterized by forgetfulness, confusion, a lack of concentration and mental clarity, is a prevalent state reported by IBS patients, a state that has been linked to disturbances in the gut microbiota [26]. Thus, when it comes to ameliorating the assessment and treatment of patients with IBS, our understanding of cognitive features related to the gut-brain axis should be of key importance [27,28].

However, results from previous studies on cognitive function in patients with IBS are far from conclusive. In a systematic review based on 12 studies, Lam et al. (2019) reported that an attentional bias toward words with emotionally negative content was the most consistent finding in IBS patients [4]. The results gave no clear evidence for the effect on memory and executive function and pointed to several methodological limitations that prevented the authors from presenting firm conclusions. First, the clinical heterogeneity between the studies was large, and results have been presented without considering co-existing factors like anxiety, depression, and the severity of IBS. Second, the selection of neuropsychological tools has been arbitrary and narrow. Therefore, the authors called for future studies including measures covering a wide range of cognitive domains and covariates. The results from Wong et al. (2019) partly followed these recommendations. They presented results showing impairment on psychometric tests of attention (a continuous performance test) and executive function (a card sorting test) in a group of patients with IBS ($N=40$) [16], and showed that their performances were impaired and closely related to comorbid anxiety. A close relation between self-reported symptoms of anxiety and self-reported executive function in IBS patients was supported in a recent study [29], and impaired cognitive test performance in patients with anxiety [30–32] and depression [30,33,34] has been shown in several previous studies. The relation between self-reported symptoms of depression and anxiety and performance on psychometrically sound neuropsychological

tests covering a wide range of cognitive domains has, as far as we know, not been studied in patients with IBS. Knowing the implication of aberrations in neural circuitries, systemic stress response, immune activation, and gut microbiota composition on patients with IBS, it is plausible to assume that the malfunction in these biological systems also affects performance on neuropsychological tests of cognition.

The results outlined above should show that more studies are essential to draw firm conclusions about cognitive function and its relation to anxiety and depression in patients with IBS. This motivated the present study to ask participants in the Norwegian multidisciplinary Bergen Brain-Gut project to perform the sub-tests included in the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) [35] and to complete a questionnaire with items assessing symptoms of anxiety and depression. Based on prior findings we expected to find more severe symptoms of anxiety and depression and lower performance on cognitive tests in patients with IBS than in HCs, and that cognitive and emotional function would be closely related [16]. Finally, we included a measure of the severity of GI symptoms to investigate its effect on the included cognitive and emotional measures. By this, we responded to the call for studies including measures of a broad range of cognitive domains and essential covariates.

Materials and methods

Participants

The present study is part of the Norwegian Brain-Gut project, conducted at Haukeland University Hospital, Bergen, Norway [36]. The aim of this project was to obtain a better understanding of the etiology of IBS by running a multidisciplinary study including psychometric tests and a wide range of questionnaires to assess symptom severity of GI- and coexistent symptoms [36]. A group of patients with IBS and healthy controls (HCs) (total $n=128$) were included. Approximately half of the IBS patients were recruited through the outpatient clinic at the hospital and the other half through media and flyers. All HCs were recruited through media and flyers. All participants were asked to read the more detailed information provided on the project’s website (www.braigut.no). Thereafter, all participants were interviewed by a study nurse (phone call). The patients were screened according to the list of inclusion and exclusion criteria (Table 1) and offered additional clinical examinations (ultrasonography, sigmoidoscopy, gastroscopy, and blood tests). The HCs were above 18 years old and were screened by a study nurse according to the same exclusion criteria as the patients. For more information on the study design, see Berentsen et al. 2020 [36].

Measures

Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)

The participants completed the Norwegian version of RBANS [35]. From the ten tests included in RBANS, five age-corrected index scores are calculated to measure Immediate memory,

Table 1. Exclusion and inclusion criteria for patients with IBS.

Inclusion	Meet Rome-IV criteria: reporting recurrent abdominal pain on average at least 1 day per week during the last 3 months, and associated alteration in bowel habits with duration for at least 6 months prior to diagnosis. IBS-SSS score above 175. Normal (Norwegian) diet for the last 3 weeks before inclusion
Exclusion	No pharmacological treatment affecting the GI tract, including medication for anxiety and depression. No presence of other organic diseases such as diabetes, coeliac disease, IBD, Polycystic ovary syndrome, active Helicobacter pylori infection, Parkinson's disease, amyotrophic lateral sclerosis, or a psychiatric disorder dependent on pharmacological treatment with known gastrointestinal side-effects. Treated with antibiotics for the last 3 months. Diets such as vegetarian or vegan. Usage of probiotics or low-FODMAP diet within the last 3 weeks. Pregnancy. Previous intestinal surgery, except appendectomy. Metallic implants not compatible with MRI, or claustrophobia. Travel outside Europe for the last 3 weeks or plan to travel in the near future.

Source: Retrieved from the BGM-project protocol [36].

Visuospatial abilities, Verbal skills, Attention, and Recall, and a total (Fullscale) index score is calculated from performance on all ten tests (Figure 1). The index scores are adjusted according to Scandinavian norms, with 100 as the mean value and 15 as one standard deviation (SD), where higher scores equal higher performances. The A-version of the test was presented to all participants according to the standardized instructions presented in the manual. The test takes about 20-30 min to complete.

The Hospital Anxiety and Depression Scale (HADS)

The participants were asked to complete the HADS, a self-assessment scale used to assess severity of symptoms used to define anxiety and depression, calculated as the sum across 14 questions related to mood disorders, with a max total score of 42 [37]. The questions are related to emotions and behaviors experienced during the previous week. The 14 questions are divided into two subscales, one for anxiety (HADS-A) and one for depression (HADS-D), with 7 questions included in each. Each subscale provides a maximum score of 21. According to the results on each of the two subscales, the participants were categorized as either a non-case (<8), a doubtful case (8-11), or a case (>11). The HADS questionnaire was completed on an online platform within the same week as the participants performed the RBANS.

IBS-Severity Scoring System (IBS-SSS)

IBS-SSS [38] was included to determine the severity level of GI symptoms associated with IBS. The questionnaire consists of 5 items related to IBS symptoms, with measures of frequency and intensity of abdominal pain, the severity of abdominal distension, dissatisfaction with bowel habits, and the interference of IBS with daily life, each with a maximum score of 100 points. The severity level of an IBS case is defined according to the IBS-SSS score as normal (0 – 74), mild (75-175), moderate (175-300) and severe (>300) and is shown to be valid and sensitive to change. Most participants

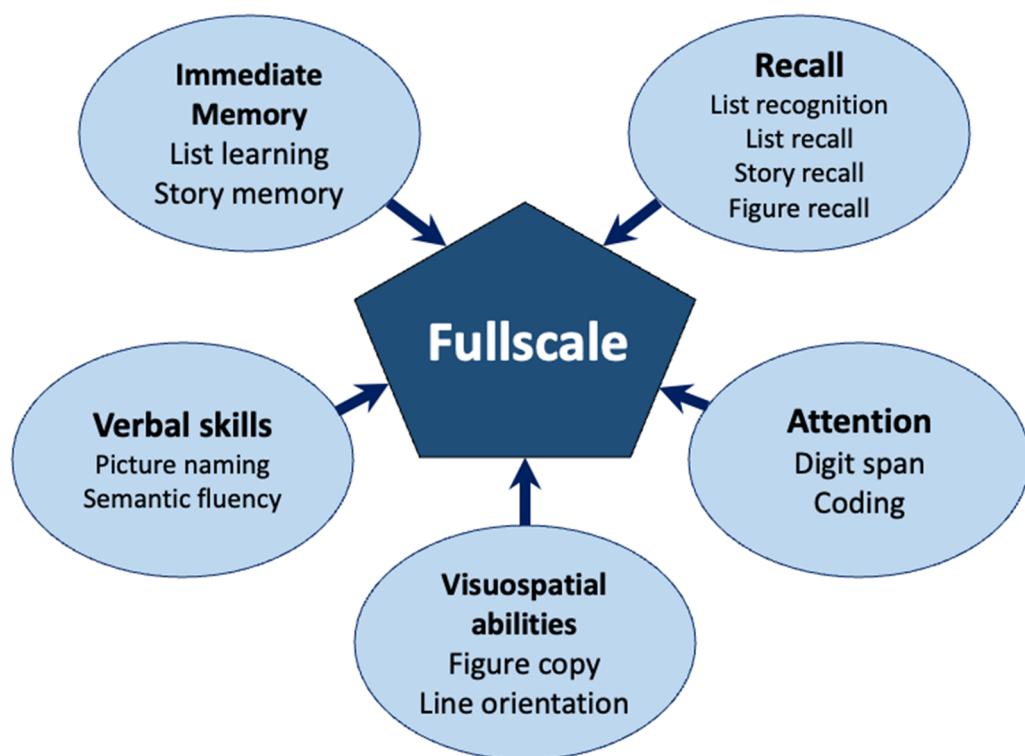


Figure 1. The five cognitive domains, each with two subtests, and the total Fullscale score calculated from performance on the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS). Inspired by a figure presented by Randolph et al. [35].

answered the questions on an online platform, except for the first six, who completed a paper version. The inclusion criteria for IBS patients in the Bergen Brain-Gut project was an IBS-SSS score ≥ 175 (Table 1). In the control group, the IBS-SSS scores were primarily in the normal range, with only a few HCs reporting a score within the lower range of the mild IBS-SSS category. The two groups were by this clearly separated by their IBS-SSS score.

Statistical analysis

Jamovi, version 2.3.21.0 was used to conduct the statistical analyses. An independent samples t-test was used to compare the results in the two groups, with the assumption that the IBS-group would perform at a lower level on the RBANS tests and that they would report higher scores on the included questionnaires (HADS and IBS-SSS) compared to the HC group. The significance level was set to $p = .05$, and Cohen's d was defined as small when $d \leq 0.2$, moderate when $d = 0.5$ and high when $d \geq 0.8$ [39]. A correlation analysis was computed to investigate relations between the RBANS indexes and the self-reported symptoms on the HADS and the IBS-SSS scales.

Results

Demographics

Of the 128 participants included in the Bergen Brain-Gut project, 102 participants performed all RBANS subtests, 65 with an IBS diagnosis (see Figure 2 for more details). Of the

102 participants, 26 were males and 76 were females. The overall mean age 38 was ($SD = 11.49$) in the IBS group and 35 ($SD = 12.3$) in the HC group. The group differences in gender and age were statistically non-significant ($p > .05$). In total, 128 participants were registered at the beginning of the study, and 26 participants were excluded from the study during the interview with the study nurse. The remaining 102 participants performed the RBANS tests, while 78 of the 102 also completed the items of the HADS and IBS-SSS questionnaires. Among the 61 patients with IBS who completed the IBS-SSS, 22 were defined as IBS with predominant diarrhea (IBS-D), 8 with predominant constipation (IBS-C), and 31 with a mix of the two (IBS-M).

Cognitive function

The IBS group obtained a significantly lower score on the Fullscale index than the HC group (see Table 2). When the results within the five domains were analyzed separately, significant results with moderate effect sizes were shown for the two memory indexes (Immediate memory and Recall). A more detailed analysis defined impairment as a score of at least one standard deviation below the age-corrected normative mean on each of the indexes. Figure 3 shows that the percentage of participants with such a low score was almost 40% for the Immediate memory index in the IBS group, with higher percentages in the IBS relative to the HC group also on the Attention and Recall indexes. The Gaussian distribution of RBANS scores gives an expected percentage of $\sim 16\%$ falling one standard deviation (SD) below the population mean on each subscale. Almost all HCs obtained a score

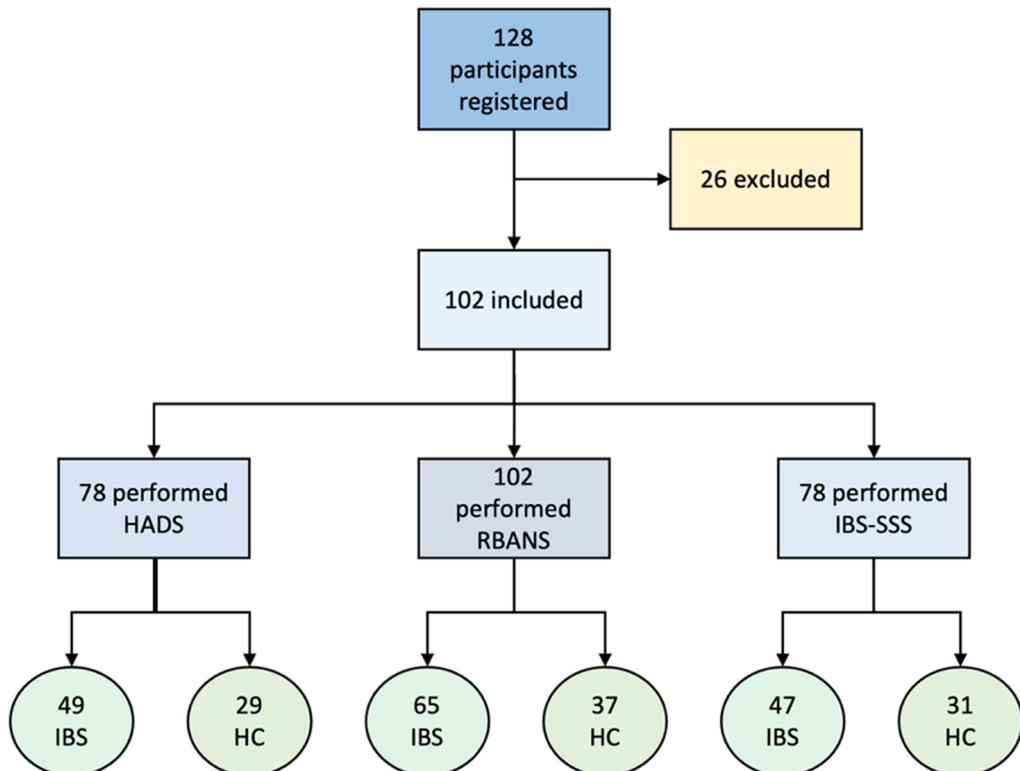


Figure 2. Flow chart showing the recruitment process.

Table 2. Results on the RBANS indexes and self-reported symptom scores on the HADS and the IBS-SSS scale.

	Mean (SD)	Mean (SD)	p	d
Emotion (HADS)				
Depression*	4.70 (3.08)	2.00 (2.06)	<.001	1.16
Anxiety	8.05 (4.21)	4.06 (2.98)	<.001	1.05
Total	12.8 (6.34)	6.06 (4.62)	<.001	0.98
Cognition (RBANS)				
Immediate Memory	89.6 (16.1)	98.3 (15.7)	.010	.54
Visuospatial*	94.0 (11.7)	94.6 (12.4)	.740	.05
Verbal Skills	98.2 (14.1)	101 (13.9)	.337	.20
Attention*	92.5 (12.2)	100 (18.3)	.111	.51
Recall*	93.2 (15.0)	102 (19.8)	.003	.51
Fullscale	90.5 (13.2)	99.2 (12.9)	.002	.67
IBS Severity				
IBS-SSS score*	274 (71.3)	35.1 (29.8)	<.001	4.03

Abbreviations: HADS: The Hospital Anxiety and Depression Scale, RBANS: Repeatable Battery for the Assessment of Neuropsychological Status, IBS-SSS: IBS-Severity Scoring System.

*Mann-Whitney test due to sig. normality test (Shapiro-Wilk).

above this cut-off score on the Fullscale index, while the percentage below this score was much higher for the IBS than the HC group (33.8 versus 16.2%). Among the patients with such a low Fullscale RBANS score, we found that 77% had IBS-M. Further, the mean IBS-SSS score in this group was as high as 280 (SD = 81).

Emotional function

The HADS questionnaire was completed by 78 participants, 49 patients with IBS and 29 HCs. The IBS group reported significantly higher scores, with large effect sizes, on the HADS compared to the HC group (see Table 2). Within the IBS group, 10 patients were defined as doubtful cases of anxiety and 5 with depression, while 16 and 2 patients were defined as severe cases of anxiety and depression, respectively. All cases with depression were also defined as doubtful ($n=2$) or severe cases ($n=5$) of anxiety. Within the group of 16 patients defined as severe cases of anxiety, the mean IBS-SSS score was 306 (SD = 77). When the doubtful cases were included, the mean IBS-SSS score was 296 (SD = 69). In the doubtful/severe anxiety group, 59% were defined as

IBS-M. No cases of anxiety and depression were identified in the control group.

IBS severity and its relation to emotional and cognitive function

In order to assess severity of GI symptoms, the IBS-SSS questionnaire was completed by 78 participants, 47 patients with IBS and 31 HCs. Table 2 shows that the IBS-SSS score was, as expected, much higher in the IBS than in the HC group ($d=4.15$), with a mean score = 35.1 and a maximum score = 108. Within the IBS group, the IBS-SSS score correlated at a statistically significant level with the HADS Anxiety score ($r = .38, p = .004$) and at a somewhat weaker level with the total HADS score ($r = .31, p = .021$). The IBS-SSS score did not correlate significantly with any of the RBANS index scores (see Figure 4).

When both groups were included in a correlation analysis, the results showed statistically significant correlations between the IBS-SSS score and the Fullscale ($r = .31, p = .003$), the Immediate memory ($r = .26, p=.013$) and the Recall ($r = .23, p = .026$) RBANS indexes. A stronger correlation was found between the IBS-SSS and the total HADS score ($r = .55, p <.001$), at a similar level both for the HADS Anxiety ($r = .54, p <.001$) and the HADS Depression subscales ($r = .42, p <.001$).

Correlations between emotional and cognitive function

Within the IBS group, neither the Fullscale RBANS score nor any of the domain specific RBANS indexes correlated significantly with any of the HADS scores. The correlations were somewhat stronger for the HADS Depression score in the HC group for the Immediate memory ($r = .35, p =.044$) and the Visuospatial indexes ($r = .37, p = .036$). The distributions of results within the two groups are illustrated by the regression lines in Figure 5.

The correlations were also weak, but at a level of significance $<.05$ between the RBANS and HADS scores when all participants (IBS and HCs) were included in the analyses.

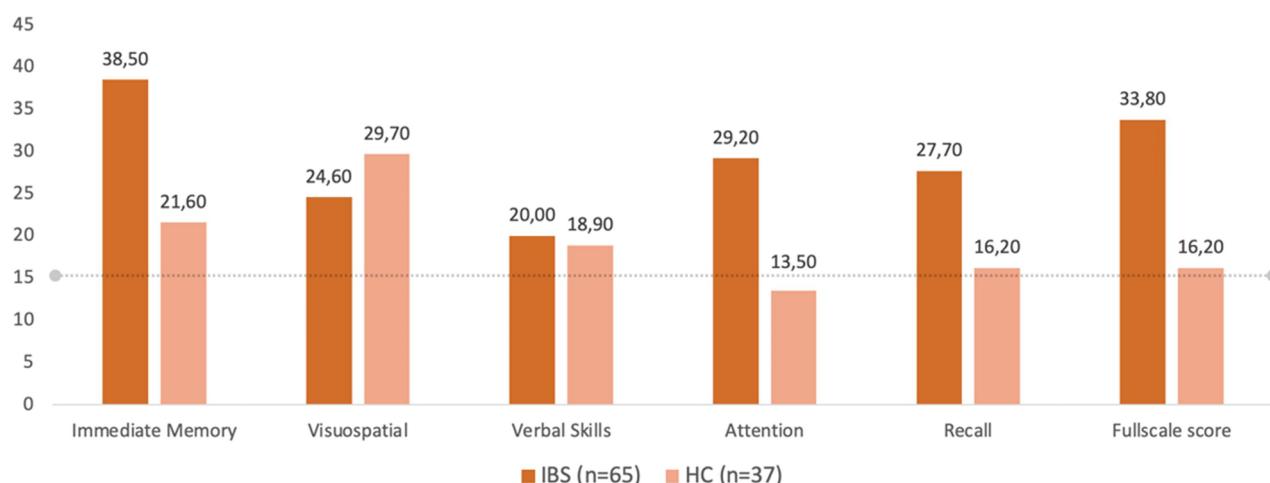


Figure 3. Percentage of IBS patients and HCs with scores equal to or below 85 on the RBANS indexes. According to a Gaussian distribution, 15.8% of the participants are expected to obtain such a score on each bar, illustrated by the dotted line.

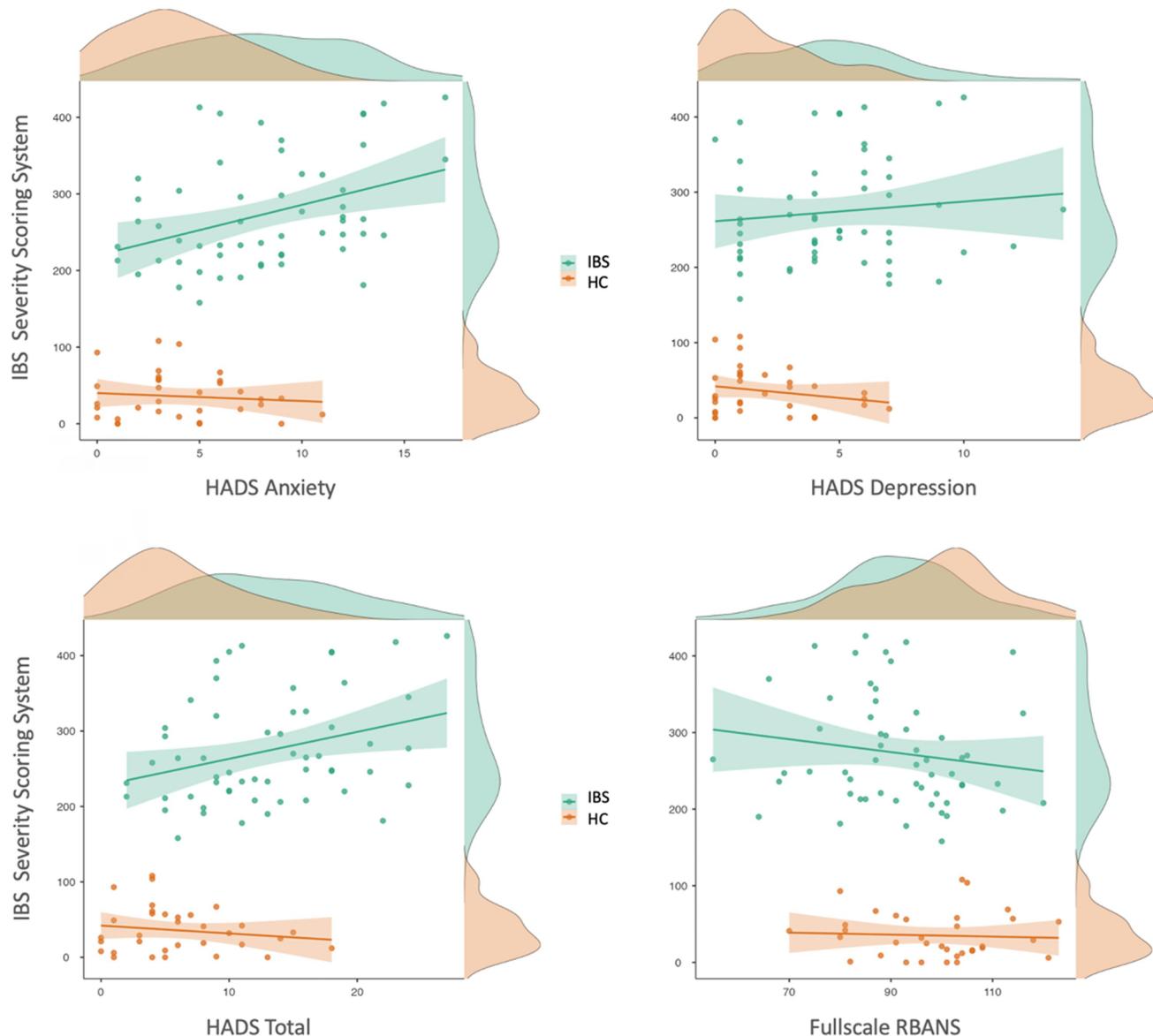


Figure 4. Scatter- and density-plots showing the associations between IBS-SSS score and the emotional and cognitive test scores for each group (green: IBS group, orange: HC). Within the IBS group, only the correlations between IBS-SSS and HADS Anxiety ($r = .38, p = .004$), and IBS-SSS and HADS Total Score ($r = .31, p = .021$) were statistically significant. Abbreviations: HADS: the Hospital Anxiety and Depression Scale, RBANS: Repeatable Battery for the Assessment of Neuropsychological Status, IBS-SSS: IBS-Severity Scoring System.

This was found both between the Fullscale RBANS index and the HADS Anxiety ($r = .26, p = .012$), the HADS Depression ($r = .24, p = .021$), and the Total HADS score ($r = .28, p = .007$), between the Immediate memory index and the HADS Anxiety ($r = .23, p = .031$) and the HADS Total score ($r = .21, p = .045$), and between the Recall index and the HADS Anxiety ($r = .22, p = .039$), HADS Depression ($r = .24, p = .024$) and the HADS Total score ($r = .25, p = .018$).

Discussion

The current study showed that the group of patients with IBS obtained lower performances than the HC group on a battery of psychometric tests assessing core cognitive domains. A large percentage of the IBS patients were categorized as impaired, meaning their performance was one standard

deviation below the population mean on the total RBANS Fullscale index. The IBS patients also reported higher scores on a questionnaire assessing symptoms of anxiety and depression, with 45% being defined as severe or doubtful cases. Notably, correlations between the cognitive and emotional measures were unexpectedly low within the IBS group. Associations with the severity of GI symptoms, as assessed by the IBS-SSS, were strong for the emotional, but weak for the cognitive measures.

The high incidence of anxiety in the IBS group aligns with results from several previous studies. Presently, the Rome criteria used to diagnose IBS tend to overlook the large number of IBS patients meeting the diagnostic criteria for anxiety and depression, and vice versa. However, detailed patient histories disclose symptoms of abdominal discomfort paired with anxiety and psychological distress, sometimes tracing back to early

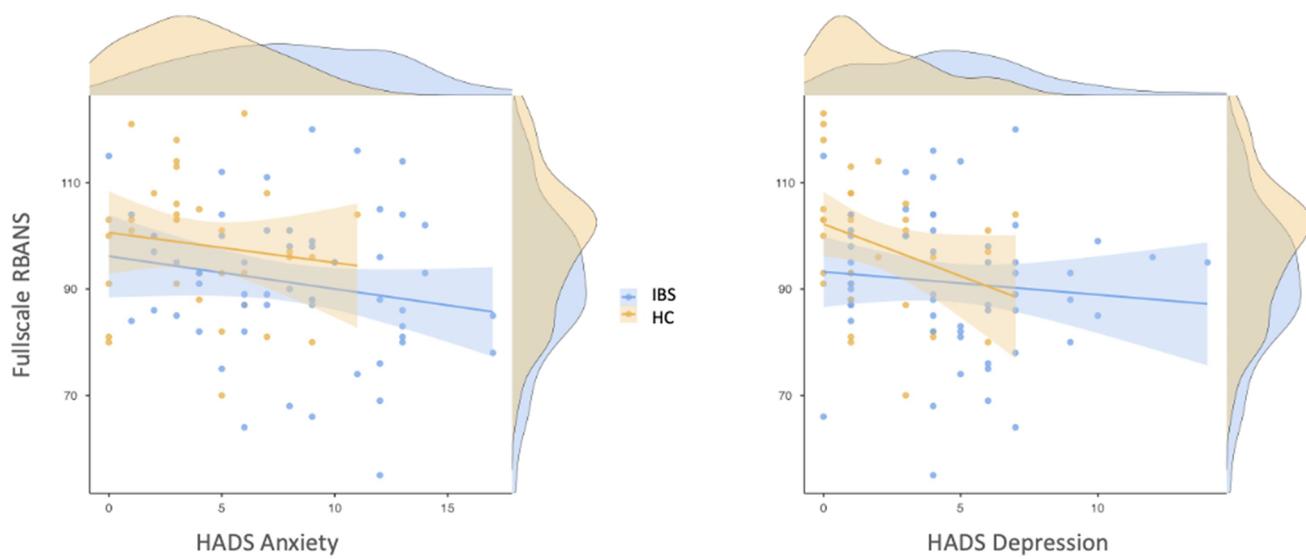


Figure 5. Scatter- and density-plots showing the correlations between the Fullscale RBANS index and the HADS Anxiety score and the Fullscale RBANS index and the HADS Depression score. The blue dots show the scores of the IBS patients and the yellow dots show the score of the HCs. The correlations are statistically significant ($p < .05$) when both groups were included in the analysis, but not when the IBS and the HC group were analyzed separately.

childhood [14]. A recent genetic epidemiological study provides a compelling rationale for the simultaneous presence of abdominal and psychological distress in IBS patients. The study identified a robust genome-wide correlation between the risk of IBS and anxiety, neuroticism, and depression [8]. These new findings support the idea that genetic predispositions can affect both the central and enteric nervous systems. This challenges the notion that emotional factors may directly cause IBS symptoms or that chronic IBS gut symptoms lead to anxiety and depression. Instead, the findings favor a shared pathophysiology between IBS (or gut microbiota) and psychiatric disorders [6,14].

The main contribution of the present study was to show that IBS patients may show impaired results on a psychometric test battery that evaluates core domains of cognitive function. Weak correlations between emotional and cognitive function were among the most unexpected findings, partly in conflict with results reported by Wong et al. [16] and Lundervold et al. [29]. The results rather suggest a kind of independence between emotional and cognitive function, at least when the latter is assessed by a neuropsychological test battery. In that impairment of each is expected to pose challenges in the everyday life of a patient with IBS, we advocate for the inclusion of both in clinical examinations. The weak correlations between severity of GI symptoms and performance on cognitive tests in the IBS group stand in contrast to the strength of the correlation between GI severity and severity of anxiety symptoms.

The notable high IBS-SSS scores among patients with IBS defined with an impairment on the Fullscale RBANS index should inspire further identification of subgroups of patients with IBS. Furthermore, the results could have been improved by inclusion of participants along the full spectrum of IBS-SSS scores. In the present study, most participants in the HC group reported from zero to symptoms at a very mild severity level, while patients with IBS were all defined with more

severe symptom scores. A spectrum view is well supported by studies showing that even otherwise healthy individuals tend to have some degree of gut discomfort. The impact of this discomfort on cognition is shown in studies on pain, where GI symptoms commonly interfere with cognitive functions [40] and influence how pain is coped with [41]. It is also well-established that GI symptoms in otherwise healthy adults are associated with poorer cognitive performance [42]. Further studies designed to cover the full spectrum of IBS-SSS scores are thus called for. Such studies may not only show stronger associations between IBS severity, cognitive and emotional function, but may also provide insights into their interplay. Such information would be crucial to facilitate more personalized treatment of patients with IBS. For dietitians and other healthcare professionals, being aware of possible cognitive limitations and their interactions with emotional and GI-related symptoms in a patient would be vital when introducing new treatment. Although psychological interventions, such as cognitive behavioral therapy (CBT), have been effective in treating patients with IBS [43], one might speculate that the efficacy partly depends on the cognitive function of the participant [44]. This consideration should also apply to other treatment options.

IBS is recognized as a multifaceted and highly heterogeneous disorder. Our results show the broad array of responses and performances in the IBS group on the questionnaire and the cognitive test, respectively. This underlines the importance of comprehensive clinical phenotyping. Subgrouping IBS patients could address the disorder's inherent heterogeneity, moving beyond a definition primarily anchored in GI symptoms and encompassing cognitive and emotional function.

Strengths and limitations

To the best of our knowledge, this is the first study directly investigating results on a psychometric instrument like

RBANS in patients with IBS. With a subgroup of patients performing at a level indicating impairment, there should be strong arguments for assessing cognitive function, at least before deciding on an appropriate treatment for a patient with IBS.

Several limitations should be mentioned. The sample size is an obvious limitation in a study of a disorder where several factors and mixtures thereof are shown to influence symptom reports [45,46]. Future studies are thus indeed needed to further explore the implications of cognitive and emotional problems suggested by the present data from the Bergen Brain-Gut project. It is worth considering the presence of sex bias against males as another limitation, although this likely reflects the overall higher prevalence of females among IBS patients. Another limitation is the absence of data on fatigue, sleep, and other psychological stressors, factors with obvious potentials to influence symptom reports. When it comes to IBS symptoms, the study implemented strict criteria for inclusion and exclusion, resulting in a sample where the IBS-SSS score could effectively differentiate the IBS versus HC group. The conclusions may therefore be restricted to patients with the most severe gastrointestinal symptoms. Lastly, it should be noted that the RBANS norms are estimated from a sample of participants with high levels of education and IQ [47]. This means that the RBANS norms will be most accurate when the participants have high levels of education. In our study, the participants on average have 16 years of education, which aligns with the normative data. By including only two tests within each cognitive domain, the RBANS cannot assess more fine-graded characteristics of cognitive function in our patients.

Conclusion

Our study showed that at least a subgroup of patients with IBS exhibits impaired performance on psychometric tests of cognitive function. Interestingly, this performance level was only weakly associated with the symptoms of anxiety and depression that characterize this patient group. Consequently, the findings contribute to underscore the importance of addressing both emotional and cognitive issues when assessing and treating patients with IBS. Future studies should build on these findings by assessing cognitive and emotional function in a larger cohort of patients with IBS, incorporating a broader spectrum of measures linked to the disease, and including statistical methods to identify subgroups and further evaluate the generalizability of the results.

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Disclosure statement

The authors declare no conflicts of interest.

Informed consent statement

Informed consent was obtained from all subjects involved in the study.

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