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Research report

Cognitive impairment in Irritable Bowel Syndrome (IBS): A systematic review

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HIGHLIGHTS

- IBS patients are more likely to have attentional bias towards GI sensation words and emotionally negative words.
- The evidence on cognitive impairment was either inconclusive or insufficient in other cognitive domains.
- Confounding factors such as age, anxiety and depression should be considered in future studies.

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ABSTRACT

Background: Irritable Bowel Syndrome (IBS) is a common functional gastrointestinal disorder which is characterized by altered bowel habits. A growing number of studies investigate the association between IBS and cognitive impairments. Current studies report conflicting results regarding cognitive impairment in IBS patients. We therefore conducted the first systematic review to examine the association between IBS and cognitive impairment and identify the types of cognitive domain involved.

Study design: Eight databases (MEDLINE, CINAHL, EMBASE, Cochrane Library, PsycINFO, ScienceDirect, China National Knowledge Infrastructure (CNKI), and Chinese Biomedical Literature Database (CBM)) were searched from the inception date up till 15 February 2018. Observational studies published in English or Chinese were independently appraised, and data was extracted, by two reviewers using the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Analytical Cross-Sectional Studies. The findings were synthesized using a narrative approach.

Results: Twelve studies met the inclusion criteria. Our findings suggested that IBS patients exhibited attentional bias towards GI sensation words and emotionally negative words. There was insufficient evidence of evidences to show that IBS patients had cognitive deficits in memory, intelligence, executive functions and general cognitive functions. A number of limitations were identified, including small sample, limited cognitive domain inclusion, lack of study details, and management of confounding variables.

Conclusion: There is evidence of attentional bias in individuals with IBS; the evidence on cognitive impairment was either inconclusive or insufficient in other cognitive domains. Further studies are needed to confirm prevalence rates and examine potential mechanisms.

1. Introduction

Irritable Bowel Syndrome (IBS) is a functional gastrointestinal disorder that is associated with altered bowel habits and characterized by a group of symptoms including abdominal pain, constipation, urgency to have a bowel movement, and incomplete evacuation over at least 3 months (Drossman and Hasler, 2016). IBS is diagnosed based on presence of physical symptoms in the previous 12 months. Currently, there is no gold standard for diagnosing IBS; but several sets of symptom-based diagnosis guidelines exist such as the Rome criteria (the

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most recent update being Rome IV in 2016) and the Manning criteria (Canavan et al., 2014; Chandar, 2017). The estimated global prevalence of IBS is 11.2%; and published prevalence rates in different countries vary based on the diagnostic criteria (Lovell and Ford, 2012b). IBS exists in all age groups. IBS prevalence is 25% lower in people older than 50 years old than in people aged 50 or younger (Lovell and Ford, 2012b; Tang et al., 2012). The prevalence is 67% higher in women than in men (Lovell and Ford, 2012a).

Patients with IBS often demonstrate several comorbid disorders. The most common non-gastrointestinal and non-psychosocial comorbid disorders include fibromyalgia, chronic fatigue syndrome, and chronic pelvic pain (Whitehead et al., 2002). Patients with IBS may also have coexisting psychosocial disorders especially anxiety, depression, and somatoform disorders (Fond et al., 2014; Gros et al., 2009; Lee et al., 2017).

A growing number of researchers are conducting studies to examine the association between IBS and cognitive function. The study authors speculate that IBS is associated with cognitive impairment, especially in the areas of executive function, memory, intelligence and attention. (Chapman and Martin, 2011; Dancey et al., 2009; Kennedy et al., 2014; Posserud et al., 2009; Rey et al., 2009; Wang et al., 2017). While it remains unclear how changes in gastrointestinal tract environment affect brain function, two theories have been proposed. First, the 'brain-gut axis' theory suggests that there is a bidirectional, constant communication between the brain and the gastrointestinal tract, and this process involves neural, immune, endocrine, and metabolic signaling. Any dysregulation in the gastrointestinal tract can have a negative impact on the brain, leading to impairment in early brain development, adult neurogenesis and even dementia (Kennedy et al., 2012; Kowalski and Mulak, 2019; Weaver et al., 2016). A second theory suggests that IBS patients might experience cognitive impairment because of its close relationship to anxiety and pain, which are common symptoms in IBS patients (Kennedy et al., 2012; Kennedy et al., 2014). Interestingly, a study found an association between IBS and cognitive deficit even after adjusting for confounders such as anxiety. This suggests that the pathological changes in the GI tract can have a direct effect on the brain to induce cognitive impairment (Attree et al., 2003).

Cognition is the mental process of acquiring knowledge and understanding through thoughts, senses and experiences. It can be classified into several key domains: attention, memory, executive function, and intelligence (Banich, 2011; Lezak, 2012). People with cognitive impairment have difficulty in concentration, making decisions, remembering, and learning. For individuals to maintain their quality of life, and perform daily activities independently, they need to maintain normal cognitive function.

Research evaluating the relationship between IBS and cognitive impairment is still evolving. Available studies focus on different cognitive domains. For example, Kennedy et al. (2014) found that IBS was associated with deficits in visuospatial memory functioning; and this relationship remained significant even after patients with psychiatric comorbidities were removed from the analysis (Kennedy et al., 2014). On the contrary, conflicting results have been reported for intelligence and executive function (Dancey et al., 2009; Kennedy et al., 2014; Rey et al., 2009; Wang et al., 2017). Although increasing evidence suggests that cognitive impairment may occur in patients with IBS, current findings vary widely across studies. The wide variety of available cognitive assessment tools, and the interrelated nature of cognitive domains prevent researchers from making solid conclusions on this topic.

Considering the high prevalence of IBS and the severe impact cognitive impairment can have on an individual, we believe that a proper and systematic analysis on their association is needed. The aims of this systematic review are: 1) to examine the association between IBS and cognitive impairment by summarizing primary studies that have examined this relationship; and 2) to identify the cognitive domains affected in patients with IBS.

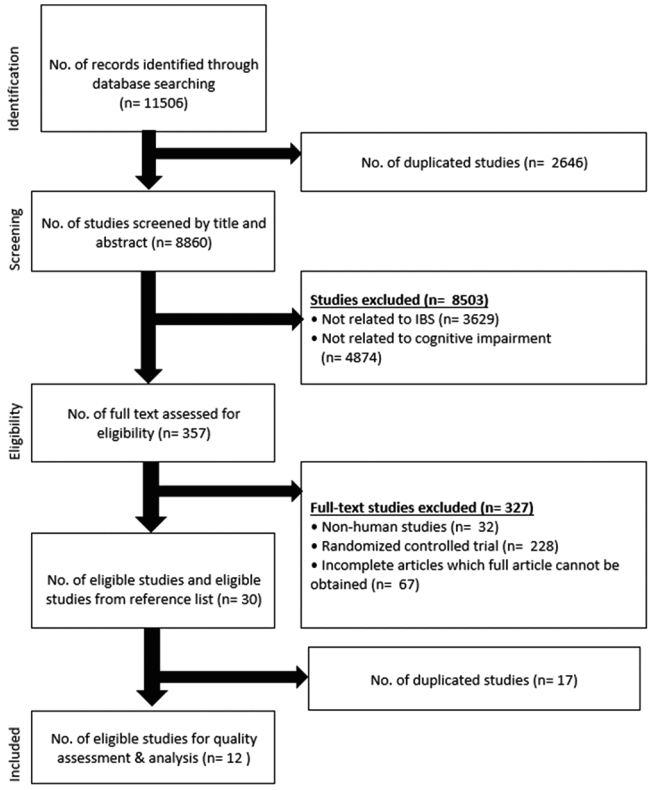

Fig. 1. Identification and selection. PRISMA flowchart showing process of inclusion and exclusion of studies.

2. Results

2.1. Study selection and characteristics

The literature search identified 11,506 studies. After removing 2646 duplicated studies, 8860 studies were screened at the title and abstract level. Following the exclusion of 8503 ineligible studies, 357 studies and their reference lists were reviewed in full-text. Twelve studies fulfilling the inclusion criteria were included in the review. Details are presented in Fig. 1.

Table 1 shows the characteristics of the included studies. All studies were cross-sectional studies, with sample sizes ranging from 29 to 231 participants. Only 3 studies had over 100 participants. Of the included studies, 6 compared IBS with healthy control groups (Afzal et al., 2006; Aizawa et al., 2012; Hubbard et al., 2015; Rey et al., 2009; Wang et al., 2017), while 6 studies included had more than one comparison group including inflammatory bowel disease (IBD), Crohn's disease, organic GI disease, depression and asthma (Attree et al., 2003; Berrill et al., 2013; Dancey et al., 2009; Gibbs-Gallagher et al., 2001; Gomborone et al., 1993; Kennedy et al., 2014). Most of the studies were conducted in UK (Afzal et al., 2006; Attree et al., 2003; Berrill et al., 2013; Chapman and Martin, 2011; Dancey et al., 2009; Gomborone et al., 1993; Kennedy et al., 2014); two studies were done in USA (Gibbs-Gallagher et al., 2001; Hubbard et al., 2015); and one was done in China (Wang et al., 2017), one was conducted in Japan (Aizawa et al., 2012), and one was conducted in Spain (Rey et al., 2009).

2.2. Participants characteristics

All the included studies consisted of 409 participants diagnosed with IBS. The proportion of female participants ranged from 50% to 100%. One study did not report on gender (Dancey et al., 2009). The mean age of IBS participants ranged from 21.7 to 45.3 years. The mean education level ranged from 10.27 to 14.59 years; and 7 studies did not

Table 1
Characteristics of the included studies.

Author/Location	Design	Sample (% Female)	Age (Mean ± SD), Years	Education (No. of Years)	Matched/control on covariance	Cognitive domains	Cognitive measuring Tool	Statistic result	Outcomes/conclusions
Afzal et al. (2006)/UK	Cross-sectional	IBS: 15 (73) Controls: 15 (67)	IBS: 30.6 ± 8.11 Controls: 30.3 ± 9.4	/	*Matched:* age, sex	Attention	Modified Stroop Task	NS p = 0.25	IBS participants did not have deficit in attention, but they showed slower colour-naming times for GI symptom-related words comparing to neutral words when the words were presented subliminally.
Aizawa et al. (2012)/ Japan	Cross-sectional	IBS: 30 (50) Controls: 30 (50)	IBS: 21.7 ± 3.0 Controls: 21.4 ± 1.5	IBS: 14.2 ± 1.6 Controls: 14.2 ± 1.5	*Matched:* age, sex, education	Executive Function	Wisconsin Card Sorting Test (WCST)	Sig p < 0.05	IBS participants had impairment in executive function, implicated by decrement in set-shifting abilities and altered brain activity than healthy controls
Attree et al. (2003)/UK	Cross-sectional	IBS: 27 (88.9) IBD: 16 (75) Controls: 27 (88.9)	IBS: 45.3 IBD: 40.4 Controls: 42.3	IBS: 12.3 IBD: 11.8 Controls: 12.41	*Matched:* not taking psychoactive medications, not suffering from a comorbid illness *Control on covariance:* depression, length of illness, age, sex, education	Memory/Attention/ Executive Function/ Intelligence	1) Wechsler Abbreviated Scale of Intelligence (WASI) 2) Virtual Environment Test (VE) 3) Stroop Color-word Test	Sig p = 0.001 NS (p value was not reported) NS p = 0.522	Verbal IQ deficits could be suspected to occur in IBS and IBD groups. No significant difference was shown between IBS participants and control group regarding to incidental memory; IBS or IBD participants had no significant deficit in selective attention.
Berrill et al. (2013)/UK	Cross-sectional	IBS: 40 (67) IBD: 150 (63) Controls: 41 (61)	IBS: 37.9 ± 11.7 IBD: 45.7 ± 11.3 Controls: 43.8 ± 13.4	IBS: 14.59 IBD: 14.14 Controls: 14.89	*Control on covariance:* age, sex	Executive Function/ Attention/Memory/ Intelligence	1) Stroop Color-word Test 2) National Adult Reading Test (NART) 3) Timed Verbal and Numeric Reasoning Test 4) Two-choice Reaction Time Test 5) Forward Digit-span Task 6) Episodic Memory Test	NS p = 0.318 NS p = 0.312 NS p = 0.451 NS p = 0.469 NS (p value was not reported)	IBS or IBD participants did not have an intrinsic disease process that was associated with cognitive dysfunction, regarding to the domains of executive function, attention, memory, and intelligence.

Author/location	Design	Sample (% female)	Age (Mean ± SD), Years	Education (No. of years)	Matched/Control on covariance	Cognitive domains	Cognitive measuring tool	Statistic result	Outcomes/conclusions
Chapman and Martin (2011)/ UK	Cross-sectional	IBS: 20 (90) Controls: 33 (63.6)	IBS: 31.2 ± 11.33 Controls: 27.64 ± 11.20	/	*Control on covariance:* anxiety, sex	Attention	1) Modified Exogenous Cueing Task	Sig p = 0.022	IBS participants had an atypical attention to pain words than neutral words. This attentional bias could be associated with increased pain and illness behavior.
Dancey et al. (2009)/UK	Cross-sectional	IBS: 29 (/) IBD: 29 (/) Controls: 30 (/)	IBS: 45 ± 2.8 IBD: 45 ± 3.33 Controls: 39 ± 3.31	IBS: 12.2 ± 0.39 IBD: 11.7 ± 0.36 Controls: 12.3 ± 0.38	*Matched:* mean age, education, no comorbid illness, not taking psychoactive medication *Control on covariance:* age, sex, education, anxiety	Intelligence	The Wechsler Abbreviated Scale of Intelligence (WASI)	Sig p < 0.001	There was a decrement in observed VIQ in both IBD and IBS participants when measuring against healthy controls.
Gomborone et al. (1993)/UK	Cross-sectional	IBS: 30 (66.7) Depression: 28 (66.7) Organic GI disease: 28 (66.7) Controls: 30 (66.7)	Median (range): IBS: 36 (19–64) Depression: 38 (21–64) Organic GI disease: 27 (19–54) Controls: 35 (19–60)	/	*Matched: age, sex*	Attention	Word-related Memory Test	Sig p < 0.05	IBS participants selectively recognized emotionally negative words, which could be an evidence of attentional bias.

(*continued on next page*)

Table 1 (*continued*)

Author/location	Design	Sample (% female)	Age (Mean ± SD), Years	Education (No. of years)	Matched/Control on covariance	Cognitive domains	Cognitive measuring tool	Statistic result	Outcomes/conclusions
Gibbs-Gallagher et al. (2001)/ USA	Cross-sectional	IBS: 16 (1 0 0) Asthma: 9 (89%) Controls: 8 (75)	IBS: 44.5 ± 12.4 Asthma: 39 ± 11.3 Controls: 34 ± 7.4	/	*Control on covariance:* frequency of experience of GI sensations, age, total number of words recalled	Attention	Word-related Memory Test	Sig $p < 0.001$	IBS participants recalled more gastrointestinal sensation words than other groups, implying attentional bias was existed.
Hubbard et al. (2015)/USA	Cross-sectional	IBS: 15 (1 0 0) Controls: 14 (1 0 0)	IBS: 31 ± 11.96 Controls: 31 ± 10.91	/	/	Attention	Attention Network Test (ANT)	p value was not reported	IBS participants had greater efficiency in both alerting and orienting networks than healthy controls. Enhanced alerting task performance was found to be related to symptom severity, suggesting that alertness in IBS participants may be due to pain amplification in these patients

Author/ Location	Design	Sample (% Female)	Age (Mean ± SD), Years	Education (No. of Years)	Matched/Control on COVARIANCE	Cognitive DOMAINS	Cognitive measuring tool	Statistic result	Outcomes/conclusions
Kennedy et al. (2014)/UK	Cross-sectional	IBS: 39 (84.6) Crohn's disease: 18 (38.9) Controls: 40 (72.5)	IBS: 28.21 ± 1.19 Crohn's disease: 32.67 ± 2.11 Controls: 28.3 ± 1.43	/	*Matched:* age, verbal IQ, units of alcohol consumed per week, BMI, not taking psychoactive medications or NSAIDS, no evidence of immuno-deficiency, no abdominal surgery within 6 months *Control on covariance:* anxiety, depression	Attention/Memory/ Executive Function	1) Episodic Memory Test 2) Intra-Extra Dimensional Set Shift (IED) 3) Spatial Working Memory (SWM) Test 4) Stroop Color-word Test	Sig $p = 0.04$ NS $p > 0.05$ NS $p > 0.05$ NS $p = 0.9$	IBS participants showed a subtle visuospatial episodic memory impairment which remained significant after psychiatric co-morbidity was controlled. However, IBS participants had no significant deficit in executive function, working memory and selective attention compared with the controls.
Rey et al. (2009)/ Spain	Cross-sectional	IBS: 100 (70) Controls: 100 (70)	IBS: 37.2 ± 12.6 Controls: 37.2 ± 13.1	Not specified	*Matched:* age, sex, education level, no psychiatric diagnosis requiring treatment	Intelligence	1) Wechsler Abbreviated Scale of Intelligence (WASI) 2) Constructive Thinking Inventory (CTI)	NS $p > 0.05$ Sig $p < 0.001$	There was no significant difference in verbal and performance intelligences between groups. However, IBS participants had lower experiential intelligence, which indicated that they were more likely to perceive daily life situation as being stressful.
Wang et al. (2017)/ China	Cross-sectional	IBS: 48 (54.2) Controls: 48 (56.3)	IBS: 40.05 ± 9.08 Controls: 40.71 ± 8.72	IBS: 10.27 ± 3.33 Controls: 10.46 ± 3.42	*Matched:* age, sex, education year	General Cognitive Function/ Attention/Executive Function	1) Mini-mental State Examination (MMSE) 2) Wisconsin Card Sorting Test (WCST) 3) Stroop Color-word Test (SCWT)	NS $p = 0.739$ Sig $p < 0.006$ NS $p > 0.05$	IBS participants did not have deficit in general cognitive function and selective attention, but impairment in executive function since IBS participants scored significantly lower in WCST.

Sig = significant; NS = not significant.

Table 2
Summary of cognitive assessment tools used in the included studies.

Name of cognitive assessment tool	Study reference number	General cognitive function	Cognitive domain			
			Attention	Memory	Intelligence	Executive Function
Attention Network Test (ANT)	10		X			
Constructive Thinking Inventory (CTI)	6				X	
Episodic Memory Test	2, 5			X		
Forward Digit-span Task	2			X		
Intra-Extra Dimensional Set Shift (IED)	5					X
Mini-Mental State Examination (MMSE)	9	X				
Modified Exogenous Cueing Task	3		X			
Modified Stroop Task	11		X			X
National Adult Reading Test (NART)	2				X	
Spatial Working Memory Test (SWM)	5			X		
Stroop Color-word Test	2,4,5,9		X			X
Timed Verbal and Numeric Reasoning Test	2				X	
Two-choice Reaction Time Test	2		X			
Virtual Environment Test (VE)	4			X		
Wechsler Abbreviated Scale of Intelligence (WASI)	4,6,8				X	
Wisconsin Card Sorting Test (WCST)	1,9					X
Word-related Memory Test	7,12		X			

Study reference number	Authors
1	Aizawa et al. (2012)
2	Berrill et al. (2013)
3	Chapman and Martin (2011)
4	Attree et al. (2003)
5	Kennedy et al. (2014)
6	Rey et al. (2009)
7	Gomborone et al. (1993)
8	Dancey et al. (2009)
9	Wang et al. (2017)
10	Hubbard et al. (2015)
11	Afzal et al. (2006)
12	Gibbs-Gallagher et al. (2001)

provide any information on level of education (Afzal et al., 2006; Chapman and Martin, 2011; Gibbs-Gallagher et al., 2001; Gomborone et al., 1993; Hubbard et al., 2015; Kennedy et al., 2014; Rey et al., 2009).

2.3. Cognitive domains measured

In total, 17 different cognitive assessment tools were used to measure general cognitive function and four cognitive domains, including attention, memory, intelligence and executive function. The available cognitive assessment tools vary greatly and there are controversies about which particular domains these tools assess. In view of this, we consulted an expert in psychology to map each cognitive assessment tool into the cognitive domain it best measured. A summary of the cognitive assessment tools and its corresponding domains can be found in Table 2.

2.4. Study quality

The Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Analytical Cross-Sectional Studies was applied because all eligible studies included in this review had a cross-sectional design (Moola et al., 2015). The complete checklist can be found in Appendix 1. Two reviewers (W.L. and C.L.) independently assessed the quality of the included studies. Any discrepancies were resolved by the third reviewer (N.C.L.). The JBI tool consists of 8 questions evaluating methodological concepts such as participant selection criteria, confounding factors, outcome validity and reliability. The questions were answered with choices of 'Yes', 'No', 'Unclear', or 'Not applicable'. One score was given when the answer to any question was 'Yes'. A zero score was assigned when the answer was 'No' or 'Unclear'. Thus, the maximum score was 8. The overall scores for each paper were calculated as percentages and the quality of each study was rated as high (80–100%), fair (50–79%) or low (< 50%) (Poudel et al., 2018). Of the 12 included studies, 5 were rated as high quality (score ≥ 80%) while seven were rated as fair (score 50–79%). None of the studies were rated as low quality (score < 50%). No articles were rejected based on quality assessments. A summary of the quality appraisal ratings for each study can be found in Table 3.

2.5. Results of cognitive domains

The included studies utilized various methodologies, recruited patients with different characteristics, measured different outcomes, and used different tools to measure these outcomes. For example, four groups of researchers used four different tests to measure intelligence (Table 2). These made it difficult to synthesize the data in a *meta*-analysis. Moreover, sometimes only two to three studies were included for a particular cognitive domain. In these cases, the results were usually inconsistent. We did not perform a *meta*-analysis due to the heterogeneity in metrics, outcomes, and participants. Instead, we conducted a narrative analysis of the results based on different cognitive domains.

2.5.1. General cognitive function

One paper assessed the general cognitive functions of participants without assessing any specific cognitive domain. There was no significant difference between IBS patients and healthy controls in this study (Wang et al., 2017). The study did not address confounding factors. Moreover, the study used the Mini Mental State Examination (MMSE), which is generally considered not sensitive enough to evaluate mild cognitive impairment (Trzepacz et al., 2015). Therefore, there was limited evidence to support an independent relationship between general cognitive performance and IBS.

2.5.2. Executive function

Executive functions refer to the abilities to plan actions for achieving goals. Executive function controls behaviors responsible for goal setting, set shifting, inhibition, planning subsequent stages, and evaluation (Banich, 2011). Six studies assessed the executive functions; and some of them employed more than one cognitive assessment test (Afzal et al., 2006; Aizawa et al., 2012; Attree et al., 2003; Berrill et al., 2013; Kennedy et al., 2014; Wang et al., 2017). Using the Wisconsin Card Sorting Test (WCST), two studies reported deficit of executive functions in IBS participants when compared with healthy controls after matching for age, sex and education level, but neither of them controlled for anxiety and depression (Aizawa et al., 2012; Wang et al., 2017). One study used Intra-Extra Dimensional Set Shift (IED) to measure executive functions (Kennedy et al., 2014). IED test is similar to WCST but it requires less cognitive demands on the subjects (Jazbec et al., 2007; Oh et al., 2014; Tröster, 2014). It aims to assess ability of the participant to rule acquisition and reversal (Oh et al., 2014). Interestingly, this study found no significant difference between the comparison groups (IBS, Crohn's disease and healthy controls) after adjusting for anxiety and depression. Four studies utilized the Stroop test and one study used the modified Stroop test. The Stroop test measures executive functions and selective attention (Alvarez and Emory, 2006). No significant group differences were found in all these studies (Afzal et al., 2006; Attree et al., 2003; Berrill et al., 2013; Kennedy et al., 2014; Wang et al., 2017). Notably, reduced performance in selective attention were initially found between groups in the study of Berrill et al. (2013), but the differences became insignificant after controlling for age and sex. Thus, the results did not support an association between selective attention and IBS.

Only two studies reported deficits in the executive function domain. However, the papers did not identify confounding factors or conduct further analysis on covariates. Thus, there was insufficient evidence to support an independent link between executive function impairment and IBS.

2.5.3. Memory

Memory is the capacity to retain, retrieve and use information. It can be defined according to its function, duration, and content, such as episodic memory and working memory (Banich, 2011).

Working memory refers to the limited capacity that is responsible for holding available information for temporary processing (Cowan, 2014). Two studies examined working memory in IBS patients, IBD patients and healthy controls with the working memory test (Berrill et al., 2013) and the spatial working memory test (Kennedy et al., 2014). Both studies found no significant difference between the groups after controlling for confounding factors such as age, anxiety and depression. There is insufficient evidence to support impaired working memory in IBS patients.

Episodic memory refers to recollection of events that they previously experienced (Allen and Fortin, 2013). Episodic memory test was employed in two studies (Berrill et al., 2013; Kennedy et al., 2014). No significant difference was found between IBS, IBD and healthy control groups in one study (Berrill et al., 2013). In the study conducted by Kennedy et al. (2014), patients with IBS exhibited significantly impaired visuospatial episodic memory compared to the control group after the analysis adjusted for depression and anxiety. Since the sample sizes for both studies were similar but contradictory results were reported, it was inconclusive to support impaired episodic memory occurs in IBS patients.

Incidental memory refers to memory of information without intention (Kontaxopoulou et al., 2017). One study utilized a test with computer-generated virtual environment. In the test, participants were asked to recall the positions and number of objects that they saw on computers. The study compared results between IBS, IBD patients and healthy controls (Attree et al., 2003). No significant results were found between IBS group and control group after adjusting for confounding

Table 3
Summary of the quality appraisal for the included studies using JBI critical appraisal checklist for analytical cross-sectional studies.

Study reference number	Authors	1) Were the criteria for inclusion in the sample clearly defined?	2) Were the study subjects and the setting described in detail?	3) Was the exposure measured in a valid and reliable way?	4) Were objective, standard criteria used for measurement of the condition?	5) Were confounding factors identified?	6) Were strategies to deal with confounding factors stated?	7) Were the outcomes measured in a valid and reliable way?	8) Was appropriate statistical analysis used?	Overall appraisal: Include/ Exclude/Seek further info	Score Percentage (%)	Comments (High/Fair/Low)
1	Aizawa et al. (2012)	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Include	75	Fair
2	Berrill et al. (2013)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Include	100	High
3	Chapman and Martin (2011)	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Include	87.5	High
4	Attree et al. (2003)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Include	100	High
5	Kennedy et al. (2014)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Include	100	High
6	Rey et al. (2009)	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Include	75	Fair
7	Gomborone et al. (1993)	No	No	Yes	Yes	No	No	Yes	Yes	Include	50	Fair
8	Dancey et al. (2009)	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Include	87.5	High
9	Wang et al. (2017)	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Include	75	Fair
10	Hubbard et al. (2015)	Yes	No	Yes	Yes	No	No	Yes	Yes	Include	62.5	Fair
11	Afzal et al. (2006)	Yes	No	Yes	Yes	No	No	Yes	Yes	Include	62.5	Fair
12	Gibbs-Gallagher et al. (2001)	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Include	75	Fair

factors such as depression. As only one study investigated incidental memory and its sample size was relatively small, there was limited evidence to support impaired incidental memory in IBS patients.

2.5.4. Intelligence

Intelligence is the ability to learn from experience and to adapt to, shape, and select environments. It involves the ability of reasoning, planning, problem solving, abstract thinking, complex ideas comprehension, and learning from experience. There are different aspects of intelligence (Sternberg, 2012).

Intelligence quotient (IQ) is a predictor of academic achievement and social functioning (Checa and Fernández-Berrocal, 2015). Two types of IQ were investigated in the included studies. The first type of intelligence, commonly known as Verbal IQ, is related to overall verbal intellectual abilities such as verbal reasoning and comprehension and acquired knowledge. The other type, commonly known as Performance IQ, refers to an ability to think logically and solve problems in novel situations that are independent of acquired knowledge (Nisbett et al., 2012; Sternberg, 2012). Four studies investigated intelligence in IBS patients and used measurement tools such as the Wechsler Abbreviated Scale of Intelligence (WASI) and the National Adult Reading Test (NART) (Attree et al., 2003; Berrill et al., 2013; Dancey et al., 2009; Rey et al., 2009). Two studies found that Verbal IQ and Performance IQ did not differ significantly between IBS and control groups (Berrill et al., 2013; Rey et al., 2009). Notably, IBS patients were initially found to have intelligence deficits in the study of Berrill et al. (2013), but the differences became insignificant after controlling for age and gender. The remaining two studies reported a significant deficit in Verbal IQ in IBS participants after confounding factors such as anxiety or depression were accounted for (Attree et al., 2003; Dancey et al., 2009). Conspicuously, the IQ scores for almost all IBS patients were within normal range in these two studies. In summary, it appeared that there was no relationship between Performance IQ and IBS. However, due to conflicting results, the results were inconclusive to indicate an independent relationship between Verbal IQ and IBS.

Experiential intelligence is the capacity to solve problems with accumulated knowledge and experience in different aspects (Sternberg, 2012). One study used the Constructive Thinking Inventory to measure the automatic thinking used in daily life and found that IBS patients had significantly lower levels of experiential intelligence compared to control group (Rey et al., 2009). This result suggested that IBS participants were more likely to perceive daily life situation as being stressful (Rey et al., 2009). Given that only one study investigated experiential intelligence, and it did not identify and control the corresponding confounding factors such as anxiety, there was limited evidence to conclude that a relationship between experiential intelligence and IBS exists.

2.5.5. Attention

Attention refers to the cognitive ability to select and concentrate on stimuli and it can be further divided to alertness, selective attention, and attentional bias (Banich, 2011).

2.5.5.1. Alertness and selective attention. Alertness refers to the overall readiness to deal with the incoming information that directly affects the rate at which information is processed selectively (Simard, 2001). Two studies investigated alertness. The attention network test (ANT) was used in the study by Hubbard and colleagues and found that IBS patients had shorter reaction times in alerting and orienting conditions than healthy controls. Moreover, it was found that enhanced alerting was significantly associated with severities of the symptoms in IBS patients. At the same time, patients were found to have greater activation of anterior midcingulate and insular cortices by functional MRI during alerting process. These two brain regions are considered to play important roles in attentional and cognitive control functions (Hubbard et al., 2015). However, the sample size in this study was small and confounders were not accounted for. Another study used the Two-choice reaction time test and compared the results between healthy, IBS and IBD participants (Berrill et al., 2013). No significant difference was found between groups after adjusting for age and sex. In summary, the evidence was inconclusive to support an association between alertness and IBS due to the conflicting results from these two studies.

Selective attention refers to the tendency to selectively process stimuli (Posserud et al., 2009). Four studies used the Stroop Test to investigate attention function in IBS participants and the results have already been discussed under the 'Executive Function' domain.

2.5.5.2. Attentional bias. Attentional bias, defined as paying attention to specific stimuli (Posserud et al., 2009), was investigated in four studies (Afzal et al., 2006; Chapman and Martin, 2011; Gibbs-Gallagher et al., 2001; Gomborone et al., 1993). By using a modified exogenous cueing task, Chapman and colleagues discovered that patients with IBS were significantly more biased towards pain words than neutral words and they showed quicker engagement with pain words compared with controls. Differences remained significant after adjustment for gender and anxiety. Particularly, a positive association was found between the pain bias and the number of days in physical pain over the previous month (Chapman and Martin, 2011). Two studies employed word-related memory tests which requested participants to recall the words from different categories that they were presented earlier. The numbers of recalled words in a specific category reflect the degree of attentional bias (Gibbs-Gallagher et al., 2001; Gomborone et al., 1993). In one study, negative, positive and neutral words were tested in IBS, IBD, depressed patients and healthy controls. The IBS group recognized significantly more emotionally negative words than healthy controls and IBD patients (Gomborone et al., 1993). In the other study, GI sensation, respiratory sensation and neutral words were tested in IBS, asthma patients and healthy controls. IBS participants recalled significantly more GI category words than other groups after controlling for age, frequency of experiencing GI symptoms, and the total number of words recalled (Gibbs-Gallagher et al., 2001). Another study utilized a modified Stroop test in which the healthy and IBS subjects had to complete the color-naming task with the addition of lexical stimuli using IBS symptoms related words and neutral words (Afzal et al., 2006). The findings showed no significant difference between groups. However, further analysis within the IBS groups found that the IBS patients selectively processed GI symptom-related words compared with neutral words when the words were presented subliminally. All these findings suggested that an association between IBS and attentional bias likely exists.

3. Discussion

To our knowledge, this study is the first systematic review aimed to examine whether IBS is associated with cognitive impairment. After an extensive search in various databases, 12 studies were included which assessed IBS and cognitive function across various cognitive domains. Our findings suggested that IBS patients might have deficit under the attention domain and they seemed to have attentional bias towards GI sensation words and emotionally negative words. There were inconclusive findings to show that IBS patients exhibit cognitive deficits in the domains of memory, intelligence, executive function, and general cognitive function. We discuss these in the following sections.

3.1. Theories of attentional bias and their implications

Chronic abdominal pain is commonly experienced by IBS patients. This may explain why many of them showed attentional bias towards GI sensation words and emotionally negative words (Tkalcic et al., 2014). A *meta*-analysis reported that patients with chronic pain had attentional biases to sensory pain words (Crombez et al., 2013). The

'Fear-avoidance model' suggests that attentional bias towards pain occurs when chronic pain patients perceived pain as catastrophic and threatening, which leads to excessive fear over pain (Todd et al., 2016). Ultimately, the patients become hypervigilant to pain as an attempt to avoid further pain (Crombez et al., 2012). Another possible mechanism for attentional bias may be due to the differences in brain activities among IBS patients. Hubbard et al. (2015), one of the included studies, observed that IBS patients had different activations in brain regions involving attentional and cognitive control functions during alerting process when compared with healthy control group. Such findings provided further evidence to the 'brain-gut axis' model that proposes a bi-directional linkage exists between the enteric and central nervous systems, and that dysregulation in the gastrointestinal tract can have negative impacts on the brain (Kennedy et al., 2012). Nevertheless, these mechanisms suggest that a possible independent association occurs between IBS and attentional bias, and more research is needed to confirm this relationship.

Persistent attentional bias to pain can increase symptom severity, affect health-related behaviors such as seeking medical advice more frequently, and increase vulnerabilities of patients to negative emotions (Chapman and Martin, 2011; Crombez et al., 2012). This highlights the need to raise awareness among healthcare professionals that IBS patients are likely to have attentional bias. Providing psychological support such as active listening and emotional support will be very helpful for these patients. Psychological interventions such as attention training and cognitive behavioral therapy (CBT) should be incorporated into IBS management to reduce attentional biases, pain and anxiety (Hakamata et al., 2010; Sharpe et al., 2012). CBT has been proven to be effective for reducing IBS symptoms and improving quality of life (Thakur et al., 2018). One theory suggests that IBS patients have specific skill deficits that render them vulnerable to symptom exacerbation. With CBT, the patients receive formal training in skills, including relaxation training, social skills, and exposure, for modifying maladaptive information processing errors and maladaptive behavioral responses (Radziwon and Lackner, 2017; Surdea-Blaga et al., 2016). In terms of pathophysiology, CBT may change the parasympathetic activity and vagal tone (Jang et al., 2017), which may partly explain its effect on reliving IBS symptoms.

3.2. Limitations of the existing literature

Most of the included studies showed little considerations for the effect of confounding factors. Some of these confounding factors (e.g. age, anxiety, depression, psychoactive medication used) have been shown to be associated with cognitive deficits. For example, it is known that cognitive performance declines with ages. However, the age ranges of participant were wide (> 30 years) in two included studies (Gomborone et al., 1993; Kennedy et al., 2014). Similarly, half of the included studies failed to control for anxiety or/and depression as confounding factors when interpreting their findings; and four of the included studies failed to exclude participants with previous use of psychoactive medication. Therefore, we need to interpret the findings reported very carefully. Future studies investigating the relationship between cognitive function and IBS should account for factors that may possibly confound that relationship.

The choice of neurological assessment tool is also a problem. As shown in Table 2, a large variety of neurological assessment tools were used in different studies. While this is common in the field of neurological research, this wide variety of assessment tools creates difficulties when comparing results between studies. Among the included studies, only two studies used an array of neuropsychological tests that allow detailed assessment of cognition performance in multiple domains including memory, intelligence, attention, and executive functions (Berrill et al., 2013; Kennedy et al., 2014), while most of the included studies relied on a single cognitive assessment tool only and focused on one particular domain. Furthermore, some studies employed assessment tools that were considered less sensitive in cognitive performance evaluation. For example, Wang et al. (2017) measured cognitive function primarily based on the Mini-Mental State Examination (MMSE), which is generally considered as a tool that is not sensitive enough to evaluate mild cognitive impairment (Trzepacz et al., 2015). Our study highlights the need for the use of an array of sensitive assessment instruments in future studies in order to capture the richness of cognitive functions.

Other problems include small sample sizes. There were only less than twenty IBS patients in three included studies (Afzal et al., 2006; Gibbs-Gallagher et al., 2001; Hubbard et al., 2015). Such small sample sizes may mask the potential effects and affect the reliability of the results. Moreover, no sub-group analysis was done in all the included studies. Thus, information on special group such as different age or gender group is lacking. Larger studies may increase confidence in the reliability of the results. Currently, there is insufficient Supporting information to provide a good estimation for an appropriate sample size. While one of the included studies recruited hundred IBS patients and compared them to 100 health controls, this may be used as a reference. To facilitate subject recruitment in a large scale study, researchers may consider to conduct multi-center trials in different states or different countries. A collaborative research approach to this research question is more likely to yield studies sufficiently powered to detect a true effect.

3.3. Strengths and limitations of this review

We have provided the first systematic review that investigates the association between IBS and cognitive impairment by summarizing existing studies across various cognitive domains. Our database search was done using a carefully constructed and comprehensive list of keywords targeting English and Chinese publications assessing different domains. As a result, we were able to capture more relevant studies using this approach. We only included studies on IBS patients diagnosed predominantly based on the Rome criteria and the Manning criteria. This reduces variability in participant characteristics and increases the applicability of findings to the IBS population. However, such stringent inclusion criteria may result in the exclusion of studies that may be useful in understanding the relationships of IBS and cognitive impairment. For example, studies that investigate cognitive performance in patients with similar IBS symptoms but do not fulfill our inclusion criteria might provide additional insight. Apart from this, our review has several limitations. Firstly, only studies published in English or Chinese were included, which may introduce bias. Although we did not come across any non-English or Chinese literature during our searching process, this may be because our target databases mostly publish English or Chinese articles. Secondly, most of the included studies had a small number of participants. Cognitive function was assessed using different neuropsychological tests in the included studies. The different sensitivities and specificities of each test is likely to cause heterogeneity. Meta-analysis could not be performed due to the great heterogeneity of the subjects and methods used in the included studies. Thirdly, all of our included studies were cross-sectional in design which may be subject to measurement bias as cognitive performance may vary when IBS symptoms are not active. Lastly, as IBS exists in all age groups, there was no age limit in our inclusion criteria. However, studies focused on pediatric patients could not be included. Thus, our systematic review does not provide any information for this group of IBS patients.

4. Summary of results and future research implications

We reviewed 12 studies assessing cognitive impairment in IBS patients according to different domains. Overall, we found the evidence to be inconclusive or insufficient for most domains. Only one domain, which is attentional bias, was consistently associated with IBS. Evidence from other domains was flawed for different reasons, such as

inconsistent results, failure to account for confounding factors, and use of various tools with different sensitivities. Conducting multicenter trials as part of a collaborative research effort might help with the issue of small sample sizes. Future research should also explore comprehensive assessment tools for different domains. Research investigators conducting future research on these domains should always account for confounders in their analyses.

5. Conclusion

This is the first systematic review examining the association of cognitive impairment with IBS. This evidence suggests that that IBS patients might have attentional bias towards GI symptoms and negative emotion. The evidence for other domains was inconclusive. Essential implications of future research and possible treatment directions of IBS patients in such deficit were also highlighted in the review. These are principally important given the potential harmful impact of attentional bias in IBS individuals.

6. Methods

6.1. Data sources and searches

This systematic review was performed in compliance with The Joanna Briggs Institute's Approach for Conducting Systematic Reviews of Association and the Preferred Reporting Items for Systematic Reviews (Knobloch et al., 2011; Moola et al., 2015). MEDLINE, CINAHL, EMBASE, Cochrane Library, PsycINFO, ScienceDirect, China National Knowledge Infrastructure (CNKI), and Chinese Biomedical Literature Database (CBM) were searched to retrieve studies published from each database's inception to 15 February 2018.

Comprehensive lists of keywords were formulated using Medical Subject Headings (MeSH) terms and synonyms (Supplementary Tables 1 and 2). These keywords were in both Chinese and English and focused on IBS, cognition, and four cognitive domains: (1) Attention, (2) Memory, (3) Executive Functions, and (4) Intelligence. Given the complexity of the cognitive domain classifications, the chosen classification of cognitive domains is based on the neuropsychiatric framework proposed by Lezak et al. and other scholars (Akintola et al., 2015; Kelly et al., 2017; Lezak, 2012; Scult et al., 2017)

6.2. Selection of studies

Two reviewers (W.L. and C.L.) performed the database search using combinations of keywords. They independently screened the titles and abstracts based on the following inclusion criteria: (1) Observational studies (e.g. cohort studies, case-control studies, cross-sectional studies, and longitudinal studies) involving only human participants with no limit on age, gender, and ethnicity, (2) Studies published in English or Chinese, (3) Studies involving IBS patients who met ROME I-IV or Manning diagnostic criteria or who received an IBS diagnosis from a physician. and (4) Studies reporting at least one subjective or objective measure of cognitive function in at least one cognitive domain.

The reviewers excluded case reports, letters, reviews, policy reports, commentaries, editorials, and randomized controlled trials (RCTs). The reviewers also excluded any studies with incomplete data and studies without an accessible full-length paper.

Each reviewer independently assessed full text studies to determine their eligibility for inclusion in the review. Reviewers also hand-searched references cited in eligible studies to identify any relevant studies not captured in the original search. The quality of each eligible studies was assessed using the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Analytical Cross-Sectional Studies. Quality ratings were cross-checked by the third reviewer (N.C.L.). Finally, two reviewers (H.Y.Y. and H.Y.L.) independently performed data extraction and synthesis; while a third reviewer cross-checked the entries for accuracy and completeness.

Declaration of Competing Interest

The authors have no interests to disclose.

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Appendix A. Supplementary data

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References

Afzal, M., et al., 2006. Selective processing of gastrointestinal symptom-related stimuli in irritable bowel syndrome. Psychosom. Med. 68, 758–761.
Aizawa, E., et al., 2012. Altered cognitive function of prefrontal cortex during error feedback in patients with irritable bowel syndrome, based on FMRI and dynamic causal modeling. Gastroenterology 143, 1188–1198.
Akintola, A.A., et al., 2015. Subclinical hypothyroidism and cognitive function in people over 60 years: a systematic review and meta-analysis. Front. Aging Neurosci. 7, 150.
Allen, T.A., Fortin, N.J., 2013. The evolution of episodic memory. Proc. Natl. Acad. Sci. U.S.A. 110 (Suppl 2), 10379–10386.
Alvarez, J.A., Emory, E., 2006. Executive function and the frontal lobes: a meta-analytic review. Neuropsychol. Rev. 16, 17–42.
Attree, E.A., et al., 2003. Cognitive function in people with chronic illness: inflammatory bowel disease and irritable bowel syndrome. Appl. Neuropsychol. 10, 96–104.
Banich, M.C., Compton, R.J., 2011. Cognitive Neuroscience, 3rd ed. Wadsworth, Cengage Learning, Belmont, CA.
Berrill, J.W., et al., 2013. An observational study of cognitive function in patients with irritable bowel syndrome and inflammatory bowel disease. Neurogastroenterol. Motil. 25, 918–e704.
Canavan, C., West, J., Card, T., 2014. The epidemiology of irritable bowel syndrome. Clin. Epidemiol. 6, 71–80.
Chandar, A.K., 2017. Diagnosis and treatment of irritable bowel syndrome with predominant constipation in the primary-care setting: focus on linaclotide. Int. J. Gen. Med. 10, 385–393.
Chapman, S., Martin, M., 2011. Attention to pain words in irritable bowel syndrome: increased orienting and speeded engagement. Br. J. Health Psychol. 16, 47–60.
Checa, P., Fernández-Berrocal, P., 2015. The role of intelligence quotient and emotional intelligence in cognitive control processes. Front. Psychol. 6, 1853.
Cowan, N., 2014. Working memory underpins cognitive development, learning, and education. Educ. Psychol. Rev. 26, 197–223.
Crombez, G., et al., 2012. Fear-avoidance model of chronic pain: the next generation. Clin. J. Pain 28, 475–483.
Crombez, G., et al., 2013. Attentional bias to pain-related information: a meta-analysis. Pain 154, 497–510.
Dancey, C.P., et al., 2009. Words fail me: the verbal IQ deficit in inflammatory bowel disease and irritable bowel syndrome. Inflamm. Bowel Dis. 15, 852–857.
Drossman, D.A., Hasler, W.L., 2016. Rome IV-functional GI disorders: disorders of gut-brain interaction. Gastroenterology 150, 1257–1261.
Fond, G., et al., 2014. Anxiety and depression comorbidities in irritable bowel syndrome (IBS): a systematic review and meta-analysis. Eur. Arch. Psychiatry Clin. Neurosci. 264, 651–660.
Gibbs-Gallagher, N., et al., 2001. Selective recall of gastrointestinal-sensation words: evidence for a cognitive-behavioral contribution to irritable bowel syndrome. Am. J. Gastroenterol. 96, 1133–1138.
Gomborone, J.E., et al., 1993. Selective affective biasing in recognition memory in the irritable bowel syndrome. Gut 34, 1230–1233.
Gros, D.F., et al., 2009. Frequency and severity of the symptoms of irritable bowel syndrome across the anxiety disorders and depression. J. Anxiety Disord. 23, 290–296.
Hakamata, Y., et al., 2010. Attention bias modification treatment: a meta-analysis toward the establishment of novel treatment for anxiety. Biol. Psychiatry. 68, 982–990.
Hubbard, C.S., et al., 2015. Increased attentional network functioning related to symptom severity measures in females with irritable bowel syndrome. Neurogastroenterol. Motil. 27, 1282–1294.
Jang, A., et al., 2017. Effects of cognitive behavior therapy on heart rate variability in young females with constipation-predominant irritable bowel syndrome: a parallel-group trial. J. Neurogastroenterol. Motil. 23, 435–445.
Jazbec, S., et al., 2007. Intra-dimensional/extra-dimensional set-shifting performance in schizophrenia: impact of distractors. Schizophr. Res. 89, 339–349.
Kelly, M.E., et al., 2017. The impact of social activities, social networks, social support and social relationships on the cognitive functioning of healthy older adults: a systematic review. Syst. Rev. 6, 259.
Kennedy, P.J., et al., 2012. Gut memories: towards a cognitive neurobiology of irritable bowel syndrome. Neurosci. Biobehav. Rev. 36, 310–340.
Kennedy, P.J., et al., 2014. Cognitive performance in irritable bowel syndrome: evidence

of a stress-related impairment in visuospatial memory. Psychol. Med. 44, 1553–1566.
Knobloch, K., Yoon, U., Vogt, P.M., 2011. Preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement and publication bias. J. Craniomaxillofac Surg. 39, 91–92.
Kontaxopoulou, D., et al., 2017. Incidental and intentional memory: their relation with attention and executive functions. Arch. Clin. Neuropsychol. 32, 519–532.
Kowalski, K., Mulak, A., 2019. Brain-gut-microbiota axis in Alzheimer's disease. J. Neurogastroenterol. Motil. 25, 48–60.
Lee, S.K., et al., 2017. The association between irritable bowel syndrome and the coexistence of depression and insomnia. J. Psychosom Res. 93, 1–5.
Lezak, M., 2012. Neuropsychological Assessment, 5th ed. Oxford University Press, New York.
Lovell, R.M., Ford, A.C., 2012a. Effect of gender on prevalence of irritable bowel syndrome in the community: systematic review and meta-analysis. Am. J. Gastroenterol. 107, 991–1000.
Lovell, R.M., Ford, A.C., 2012b. Global prevalence of and risk factors for irritable bowel syndrome: a meta-analysis. Clin. Gastroenterol. Hepatol. 10, 712–721.e4.
Moola, S., et al., 2015. Conducting systematic reviews of association (etiology): the Joanna Briggs Institute's approach. Int. J. Evid. Based Healthc. 13, 163–169.
Nisbett, R.E., et al., 2012. Intelligence: new findings and theoretical developments. Am. Psychol. 67, 130–159.
Oh, A., et al., 2014. Neuromagnetic correlates of intra- and extra-dimensional set-shifting. Brain Cognit. 86, 90–97.
Posserud, I., et al., 2009. Hypervigilance in irritable bowel syndrome compared with organic gastrointestinal disease. J. Psychosom Res. 66, 399–405.
Poudel, P., et al., 2018. Oral health knowledge, attitudes and care practices of people with diabetes: a systematic review. BMC Public Health 18, 577.
Radziwon, C.D., Lackner, J.M., 2017. Cognitive behavioral therapy for ibs: how useful, how often, and how does it work? Curr. Gastroenterol. Rep. 19, 49.
Rey, E., et al., 2009. Constructive thinking, rational intelligence and irritable bowel syndrome. World J. Gastroenterol. 15, 3106–3113.
Scult, M.A., et al., 2017. The association between cognitive function and subsequent depression: a systematic review and meta-analysis. Psychol. Med. 47, 1–17.
Sharpe, L., et al., 2012. Is there a potential role for attention bias modification in pain patients? Results of 2 randomised, controlled trials. Pain 153, 722–731.
Simard, D.W., W., 2001. Alertness, orientation, and detection: the conceptualization of attentional functions in SLA. 23.
Sternberg, R.J., 2012. Intelligence. Dialogues Clin. Neurosci. 14, 19–27.
Surdea-Blaga, T., et al., 2016. Psychological interventions for irritable bowel syndrome. J. Gastrointestin Liver Dis. 25, 359–366.
Tang, Y.R., et al., 2012. Age-related symptom and life quality changes in women with irritable bowel syndrome. World J. Gastroenterol. 18, 7175–7183.
Thakur, E.R., et al., 2018. A systematic review of the effectiveness of psychological treatments for ibs in gastroenterology settings: promising but in need of further study. Dig. Dis. Sci. 63, 2189–2201.
Tkalcic, M., et al., 2014. Attentional biases in irritable bowel syndrome patients. Clin. Res. Hepatol. Gastroenterol. 38, 621–628.
Todd, J., Sharpe, L., Colagiuri, B., 2016. Attentional bias modification and pain: the role of sensory and affective stimuli. Behav. Res. Ther. 83, 53–61.
Tröster, A.I., 2014. Clinical Neuropsychology and Cognitive Neurology of Parkinson's Disease and Other Movement Disorders. Oxford University Press.
Trzepacz, P.T., et al., 2015. Relationship between the montreal cognitive assessment and mini-mental state examination for assessment of mild cognitive impairment in older adults. BMC Geriatr. 15, 107.
Wang, J.B.Y., J.B., Dong, J.C, 2017. Executive Function Change in Patients with Irritable Bowel Syndrome (IBS). Acta Academiae Medicinae Weifang. 39, 387.
Weaver, K.R., et al., 2016. Neuroimaging the brain-gut axis in patients with irritable bowel syndrome. World J. Gastrointest. Pharmacol. Ther. 7, 320–333.
Whitehead, W.E., Palsson, O., Jones, K.R., 2002. Systematic review of the comorbidity of irritable bowel syndrome with other disorders: what are the causes and implications? Gastroenterology 122, 1140–1156.