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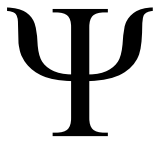

Abdominal Pain, Cognitive Function and Personality in Patients with Irritable Bowel Syndrome

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Abstract

The present study investigated and compared personality, cognitive and emotional function in patients with Irritable Bowel Syndrome (IBS) and healthy controls, and examined associations between these variables and a measure of IBS related pain. The study is part of a larger ongoing project, the Bergen Brain-Gut project (BBG), and includes data collected at baseline before January 2021. The included patients were between 18 and 65 years, and they fulfil Rome-III criteria for IBS. A total of 53 IBS patients and 34 healthy controls completed questionnaires assessing severity of IBS, here used as a measure of IBS related pain (IBS-SSS), anxiety and depression (HADS), executive function in daily life (BRIEF-A) and personality (NEO-FFI-3). They also performed a set of psychometric tests, assessing different cognitive domains (RBANS). Statistical analysis, data processing and visualization were conducted using Python and Jupyter notebooks, and the code is available on Github to support open and reproduceable research. The results showed that the IBS patients reported more severe symptoms of anxiety, depression, neuroticism and executive dysfunction in daily life and obtained lower scores within some of the tested cognitive domains than healthy controls. The IBS pain measure was found to be positively correlated with symptoms of anxiety, depression and neuroticism, and negatively correlated with the emotional control and working memory subscores from BRIEF-A and the delayed memory index from RBANS. The results suggest that temperamental, emotional, and cognitive characteristics should be assessed and considered when selecting treatment approaches for a patient with IBS.

Keywords: brain-gut-microbiota axis, irritable bowel syndrome, neurogastroenterology, psychometric tests, personality, IBS pain, working memory, delayed memory, emotional control, neuroticism, BIG FIVE, NEOPI, pain, abdominal pain, psychotherapy, ISB symptoms, negative emotions

Sammendrag

Studien undersøker og sammenligner personlighet, kognitiv og emosjonell funksjon blant pasienter med IBS og friske kontroller, og undersøker i hvilken grad disse variablene samvarierer med alvorlighet av det vi her definerer som IBS relatert smerte. Data er hentet fra et pågående prosjekt, Bergen Brain-Gut (BBG) og inkluderer data samlet inn før januar 2021. Totalt 53 pasienter med IBS ble inkludert i studien. De var mellom 18 og 65 år, og tilfredsstiller Roma-III kriteriene for IBS. IBS pasientene og 34 kontrollpersoner fylte ut evalueringsskjemaer for bl.a. alvorlighetsgrad av IBS (IBS-SS), angst og depresjon (HADS), eksekutiv funksjon i hverdagen (BRIEF-A), personlighet (NEO-FFI-3). I og med at smerte er et IBS kjernesymptom, vil IBS-SS skåren her benyttes som et mål på IBS relatert smerte. I tillegg ble kognitiv funksjon kartlagt med et testbatteri som dekker ulike kognitive domener (RBANS). Statistisk analyse, data prosessering og visualisering ble utført i Python og Jupyter notebooks, og lastet opp på Github for å støtte åpen vitenskap og reproduserbar forskning. Resultater viser at IBS pasienter rapporterte høyere grad av angst og depresjon, nevrotisisme, og eksekutiv dysfunksjon i hverdagen, og at de skåret lavere på kognitive mål enn kontroller. Det ble funnet signifikante positive korrelasjoner mellom målet på IBS relatert smerte og angst, depresjon og nevrotisisme, og negative korrelasjoner mellom IBS relatert smerte og emosjonell kontroll, arbeidsminne (BRIEF-A) og utsatt hukommelse (RBANS). Disse resultatene tyder på at personlighet, emosjoner og kognitive evner bør kartlegges og vektlegges når en velger behandling for en pasient med IBS.

Nøkkelord: Hjerne-tarm-mikrobiota-aksen, irritabel tarm syndrom, personlighet, psykometriske tester, IBS smerte, nevrotisisme, NEOPI, smerte, magesmerte, psykoterapi, IBS symptomer, negative emosjoner, arbeidsminne, utsatt hukommelse, emosjonell kontroll, kognitive evner

Contents

Introduction

The gut-brain axis has recently become a popular model for understanding somatic and psychiatric disorders. By studying the interaction between the central nervous system and the gastrointestinal tract, i.e., the gut-brain axis, we can better grasp the complexity of the human body as a whole and find new ways of understanding mental and physical health. Irritable Bowel Syndrome (IBS), defined as a functional gastrointestinal disorder, is one of the disorders characterized by a dysfunction of the gut-brain axis. Abdominal pain is one of the hallmark symptoms in IBS. The severity of this pain varies, ranging from mild to severe and crippling (Heitkemper et al., 2011). Patients with IBS commonly suffer from other disabling symptoms, including pain in the lower back, muscles and joints, nausea, headache, and constant tiredness. Chronic pain, accompanied by discomfort and embarrassment associated with IBS symptoms, is associated with mental health problems, including anxiety and depression. Furthermore, it has been shown that personality traits may play a role in the severity of the disorder (Mousavinasab et al., 2007). In the present study we included information about cognitive function. Although only a few studies have investigated cognitive function in IBS patients, we know its impact on a range of other psychosomatic and functional disorders (Lam et al., 2019; Subic-Wrana et al., 2005). From this we expect that connecting knowledge from different domains, such as personality psychology, neuropsychology and current scientific understanding of chronic pain, may help shed light on new ways we can adjust treatments and help IBS patients improve their somatic and mental health.

The current study explored associations between chronic pain, personality, and cognitive function in a sample of IBS patients participating in an ongoing project at Haukeland University Hospital, Bergen, Norway. The rationale of this inquiry is that we need to understand more about personality profiles and emotional and cognitive function of the

patients with IBS to improve treatment options, with a primary concern for its main symptom: visceral pain. This information is expected to contribute to improved understanding of how we can make treatment more effective for this patient group. Before presenting the results of the study, I will describe the definitions and diagnostic criteria for IBS, possible mechanisms underlying the disorder, the importance of personality and cognitive function in IBS, as well as current IBS treatment strategies.

Irritable Bowel Syndrome

Definitions

Irritable Bowel Syndrome (IBS) is a chronic functional gastrointestinal disorder (FGID), characterized by chronic, recurrent abdominal pain or discomfort, associated with disturbed bowel habit, in the absence of any structural abnormalities that explain these symptoms (Ford & Vandvik, 2012). IBS is the most common and best researched FGID, with an estimated prevalence of 10-15% in the population, affecting more women than men (Saito et al., 2002; Walker et al., 1998). FGIDs are the disorders of function of the gastrointestinal (GI) tract, they are not caused by structural or biochemical abnormalities. They are also called disorders of gut–brain axis and are characterized by GI symptoms related to any combination of the following: motility issues, visceral hypersensitivity, altered mucosal and immune function, altered gut microbiota, and altered central nervous system processing (Drossman, 2016).

IBS Prevalence and Comorbidity

The prevalence of IBS is higher in people with other co-existing FGID, such as functional constipation, anal incontinence, functional dyspepsia, and gastro-esophageal reflux diseases (Ford et al., 2009; Jung et al., 2007). There is also a considerable overlap between IBS and disorders like migraines, fibromyalgia, chronic fatigue syndrome, sleep disturbances, cardiac syndromes, and chronic pelvic pain (Riedl et al., 2008).

In the IBS patients, the frequency of mental disorders is also higher in comparison with the general population: for any mental disorder and for anxiety and mood disorders specifically (Stanculete & Dumitrascu, 2015). Patients with a high degree of somatic comorbidity (with other somatic diagnoses) also present higher levels of anxiety and depression, neuroticism, adverse life event and reduced quality of life (Vandvik et al., 2004). In contrast, IBS patients with low somatic comorbidity have significantly less psychological distress and health anxiety, as well as better quality of life than patients with high somatic comorbidity (Sperber et al., 1999; Vandvik et al., 2004).

Diagnostic Criteria

Different diagnostic criteria for IBS have been developed during the last four decades, including the Manning criteria (Manning et al., 1978), Kruis model (Kruis et al., 1984) and the Rome criteria (Emmanuel & Quigley, 2013). The Rome criteria have become the gold-standard for diagnosing IBS, and is also used to standardize the type of patients recruited into treatment trials (Emmanuel & Quigley, 2013). The two most recent criteria are Rome III (2006-2016) and Rome IV (from May 2016) (Drossman, 2016).

The fundamental definition of IBS based on abdominal pain in association with bowel dysfunction has been consistent since the first version of the Rome criteria for IBS were published in 1982 (Camilleri, 2020). However, two major changes occurred in the Rome III and Rome IV criteria. Starting from Rome II, the conditions that were deemed to be non-IBS were "split off", i.e. the conditions that were not consistently associated with pain, such as functional abdominal bloating, functional constipation, and functional diarrhea. Rome III subcategorized IBS based on predominant stool pattern, i.e., IBS-constipation (IBS-C), IBS-diarrhea (IBS-D), IBS- mixed (IBS-M), and unsubtyped IBS (Thompson et al., 1999). Rome IV introduced more stringent frequency criteria for the pain to be eligible for diagnosis of IBS (specifically, on average, at least 1 day per week in the last 3 months) and the exclusion of

discomfort (in contrast to pain) (Camilleri, 2020). Despite the introduction of Rome IV, Rome III are still the most widely used diagnostic criteria in the clinical setting and is also used in the current study. A summary of Rome III diagnostic criteria for IBS is presented in Table 1 (Longstreth et al., 2006).

Table 1

Rome III Diagnostic Criteria for Irritable Bower Syndrome

Recurrent abdominal pain or discomfort[a] at least 3 days per month in the last 3 months associated with 2 or more of the following: 1. Improvement with defecation 2. Onset associated with a change in frequency of stool 3. Onset associated with a change in form (appearance) of stool
Subtyping IBS by Predominant Stool Pattern • IBS-C (constipation): hard or lumpy stools for ≥ 25% of bowel movements and loose (mushy) or watery stools <25% • IBS-D (diarrhea): loose (mushy) or watery stools for ≥ 25% of bowel movements and hard or lumpy stool for <25% • IBS-M (mixed): hard or lumpy stools for ≥ 25% of bowel movements and loose (mushy) or watery stools for ≥ 25% • Unsubtyped IBS: insufficient abnormality of stool consistency to meet criteria for subtypes IBS-C, D, or M

Note. [a] Criteria should be fulfilled for the last 3 months with symptom onset of 6 months prior to diagnosis.

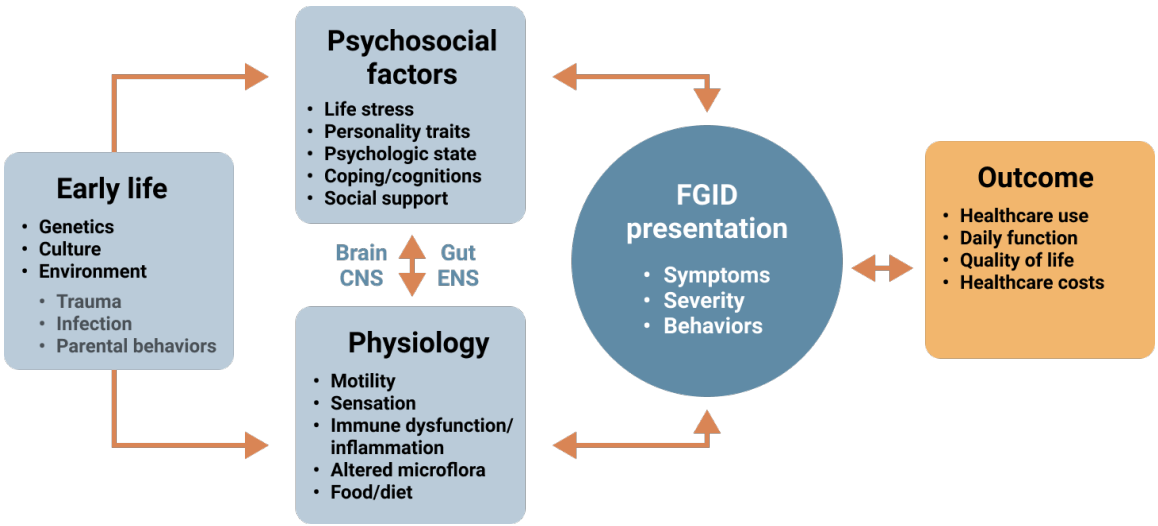
Pathogenesis of IBS

The pathogenesis of IBS remains uncertain. The proposed mechanisms include altered gut signalling which manifests as visceral hypersensitivity, abnormal pain processing in the CNS, low-grade chronic inflammation, gastrointestinal permeability and imbalances in gut microbiota (Whitehead et al., 2002). The non-intestinal comorbidities suggest that the pathophysiological mechanisms are more systemic and include the autonomic nervous system

and the brain–gut axis (Riedl et al., 2008). More than three decades ago, Engel (Engel, 1977) offered a holistic, systems theory-based biopsychosocial model, where illness was described as the product of biological, psychological and social subsystems that interact at multiple levels. According to this model it is the combination of these interacting subsystems that determines the illness (Drossman, 2016). By the end of the 1990, the concept of the brain-gut axis emerged, as well as the newer field of neurogastroenterology, which provided explanations for the structural and physiological components of the biopsychosocial model (Drossman, 2016).

Figure 1

Biopsychosocial Conceptualization of Functional GI Disorders



Note. A biopsychosocial conceptualization of functional GI disorders, showing relationship between environment, genetics, psychosocial factors, physiological functioning, and their mutual interaction (brain-gut axis). Adapted from "Functional Gastrointestinal Disorders: History, Pathophysiology, Clinical Features, and Rome IV" by Douglas A. Drossman, 2016, Gastroenterology, Volume 150, Issue 6, pp. 1262-1279.e2, (https://doi.org/10.1053/j.gastro.2016.02.032). Copyright 2016 by the AGA Institute.

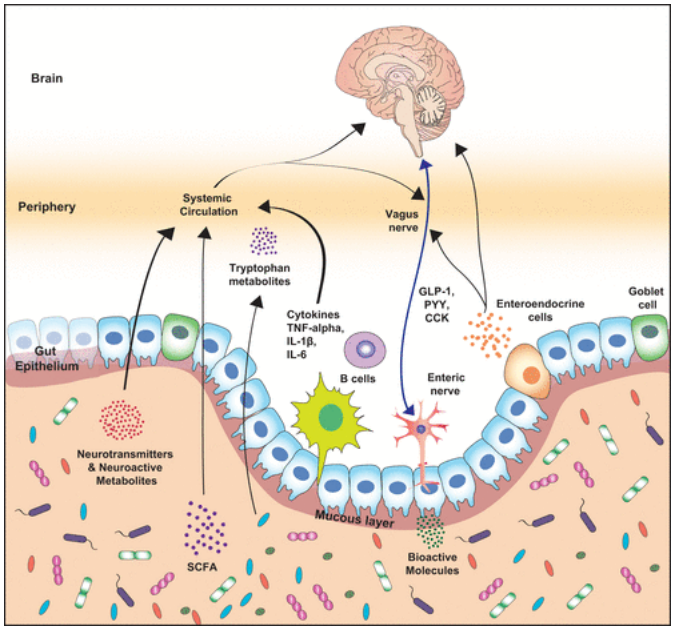
Gut Microbiota

The gastrointestinal tract is composed of 10^{13} to 10^{14} microorganisms whose collective genome ("microbiome") contains at least 100 times as many genes as our own genome (Gill et al., 2006). The average number of species in adult microbiota is around 1000 (Qin et al., 2010) with more than 7000 different strains (Ley et al., 2006). Being in the mutualistic relationship with the human host (Backhed, 2005), the gut microbiota plays a crucial role in the development and functioning of immune responses (Olszak et al., 2012; Round et al., 2010), gut motility regulation, maintaining intestinal barrier and nutrient absorption.

The two predominant bacterial phylotypes in human microbiota are Bacteroidetes and Firmicutes, with Proteobacteria, Actinobacteria, Fusobacteria and Verrucomicrobia phyla present in relatively low abundance (Eckburg, 2005). Though the population of the gut is relatively stable in an adult human, it can still be modified by different factors such as pharmaceutical treatments, environmental stressors, dietary and lifestyle changes, as well as biological aging (Eckburg, 2005). The increased understanding of how microbiota affects the gut-brain axis has led to the appreciation of a distinct microbiota-gut-brain axis. The microbiota uses different pathways to communicate with the brain including by tryptophan metabolism and microbial metabolites such as short-chain fatty acids, branched chain amino acids, and peptidoglycans (Cryan et al., 2019).

Figure 2

Pathways of Communication between Gut Microbiota and the Brain



Note. Schematic outlining the various known bidirectional pathways of communication between the gut-microbiota and the brain, including hepatic and gallbladder metabolism, immune-modulatory responses, neuronal innervation, enteroendocrine, and microbial metabolite signaling. CCK, cholecystokinin; GLP-1, glucagon-like peptide-1; IL, interleukin; PYY, peptide YY; TNF, tumor necrosis factor; SCFA, short-chain fatty acid. From "The Microbiota Gut-Brain axis" by J.F. Cryan et al., 2019, *Physiological Reviews, 99:4*, pp.1877-2013. Copyright 2019 the American Physiological Society.

Microbiota was first suggested to play a role in IBS after observing the development of IBS after an acute viral, bacterial or parasitic infection (Quigley, 2018). Deviations in gut microbiota, a dysbiosis frequency of 73% was detected among IBS patients (Casén et al., 2015). Studies comparing intestinal bacteria in IBS patients with healthy controls report increase in abundance of Proteobacteria, including *Veillonella*, and Firmicutes, including *Lactobacillus* and *Ruminococcu* (Chong et al., 2019; Rigsbee et al., 2012; Tana et al., 2010). A combination of Veillonella and Lactobacillus is known to produce acetic and

propionic acid, which are associated with abdominal symptoms, impaired quality of life and negative emotions in IBS (Tana et al., 2010). IBS patients also exhibit decreased quantity of *Bifidobacterium*, *Faecalibacterium, Erysipelotrichaceae* and butyrate- and methane-producing microorganisms (Pozuelo et al., 2015; Rajilić–Stojanović et al., 2011).

The Brain-Gut Axis

As already mentioned, there is an increased awareness that the brain-gut axis plays an essential role in IBS. The brain-gut axis can be defined as a two-way communication channel between the brain and the gut (Quigley, 2018), and represents an integrated system, monitoring and linking gut functions to cognitive and emotional centers of the brain via neural, hormonal and immunological routes (Mayer, 2011). Enteric nervous system communicates with the brain via spinal and vagal pathways as well as immune and endocrine mechanisms (Tougas, 2000), while the efferent signals from the brain to the gut are transmitted mostly through the autonomic nervous system and hypothalamic-pituitary-adrenal (HPA) axis (Kano et al., 2018).

Within the CNS, the limbic system plays a central role in gut control, emotionality, and learning as well as top-down modulation of visceral pain transmission (Jones et al., 2006). When the system is sensitized or disrupted by psychosocial or physical stress factors, it may lead to changes in pain processing. Furthermore, the dysfunction of the brain-gut axis may have pathophysiological consequences such as increased inflammation, altered stress response, chronic abdominal pain syndromes and eating disorders (Cryan & Dinan, 2012; Lyte, 2013; Mayer, 2011).

The HPA axis, which provides the core regulation of the stress response, has a significant effect on the microbiota-brain-gut axis (Bonaz & Sabate, 2009; Dinan & Cryan, 2017). In IBS, the HPA axis, and subsequently, the microbiota-brain-gut axis are dysregulated (Dinan et al., 2006). The hyperactive HPA axis may lead to changes in the microbial

composition of the lower GI tract, increase microbial pathogenicity, as well as alter the gastrointestinal permeability, motility, and visceral sensitivity (Rhee et al., 2009). Stress hormones such as adrenaline and corticosteroids can increase the virulence of enteropathogens (Cristiano et al., 2010; Cristiano & Vanessa, 2012; Karavolos et al., 2008; Winzer et al., 2011).

Patients with IBS have not only an increased prevalence of anxiety and depression (Cho et al., 2011; Karlidag et al., 2003; Wells et al., 1988), but there is an increased awareness that underlying mental conditions may actually worsen the symptoms of IBS (Cho et al., 2011). According to the biopsychosocial model (Drossman, 1999; Engel, 1977), the psychological and social factors affect gastrointestinal system through bi-directional communication between the CNS and the ENS. Anxiety and depression, as well as negative perceptions of symptoms and sickness behavior may affect gastrointestinal system directly, as well as lead to unhelpful behaviors, contributing to the exacerbation of illness over time (Deary et al., 2007). This is exemplified by results from studies showing that self-reported anxiety and depression provide a two-fold risk for IBS onset (Sibelli et al., 2016).

Chronic Pain, Emotional and Cognitive Function in Patients with IBS

One of the major symptoms of IBS is chronic visceral pain. Pain is the most common reason for help-seeking behavior in patients with IBS, and it has a strong impact on the patients' quality of life (Zielińska et al., 2018). No single mechanism can explain the cause of IBS pain – it is rather a combination of factors leading to increased pain sensation in the gut (Holtmann et al., 2016). IBS pain can be explained by various mechanisms: nociceptive signaling from the colon that leads to hypersensitivity, increased intestinal permeability and alterations in the neuroendocrine system that over-sensitize central and peripheral nervous system (Zhou & Verne, 2011). Systemic mechanisms are also at play: for example, chronic stress may influence the gut-brain axis and increase pain sensitivity by production of cortisol

and catecholamines, and subsequent release of inflammatory cytokines, such as IL-6, IL-11 and TNF-a (Hughes et al., 2014).

There is a growing body of evidence that people with chronic pain may exhibit cognitive impairments, including deficits in attentional processes (Dick et al., 2002; Grisart & Plaghki, 1999) and executive functions, such as working memory, response inhibition, mental planning and flexibility, as well as emotion regulation (Baker et al., 2016; Berryman et al., 2014; Berryman et al., 2013; Gelonch et al., 2016). It has also been shown that chronic pain leads to functional and structural cortical changes (Moseley & Flor, 2012; Wand et al., 2010), such as decreases in gray matter in frontal regions of the brain that are vital to cognitive and emotional functioning (Burgmer et al., 2009; Saab, 2014). Secondary effects of chronic pain, such as lack of sleep, anxiety and depression, may also indirectly affect cognitive function (Austin et al., 2001; Castaneda et al., 2007; Shaw et al., 2013).

Systematic reviews and meta-analysis of the effectiveness of cognitive-behavioral therapies (CBT) on chronic pain in general show weak effects of CBT on improving pain, but only immediately post-treatment and when compared with treatment as usual/waiting list (Eccleston et al., 2013; Williams et al., 2012). Behavior therapy had no effect on pain compared to doing nothing, neither post-treatment nor at follow-up. CBT but not behavior therapy has small effects on disability associated with chronic pain, as well as has some effect on mood and catastrophizing outcomes.

Studies of IBS patients have reported deficits in affective memory recall (Kilkens et al., 2004), visuospatial memory (Kennedy et al., 2014) and verbal function (Dancey et al., 2009). There are also studies showing that patients with IBS exhibit attentional bias towards GI sensation words and emotionally negative words (Lam et al., 2019). The disruption of cognitive function in IBS patients can be explained within the cognitive neurobiological model proposed by Kennedy et al (2012), suggesting a bidirectional communication between

the brain and the gut, and that IBS patients present changes in neural, immune, endocrine, and metabolic signaling (Kennedy et al., 2012). Stress (Dinan et al., 2006; Drossman et al., 2002; Mayer, 2000), immune activation (Clarke, Fitzgerald, et al., 2009; Clarke, O'Mahony, et al., 2009; Dinan et al., 2008; Dinan et al., 2006; O'Mahony et al., 2005) and chronic pain (Bouin et al., 2002; Mayer et al., 2009) are three pivotal factors affecting the disruption of the brain-gut axis and contributing to the IBS symptoms (Kennedy et al., 2012). All three factors may have impact not only on emotion- or IBS-symptom-related cognition but also on key domains of executive function, working memory, attention and episodic memory (Kennedy et al., 2012).

Stress, immune activation, and chronic pain may not only exacerbate IBS symptoms, but indirectly affect the quality of life of the patients. Problems with memory and executive functions alone can increase the risk of poor quality of life (Love et al., 2016; Sanz et al., 2018; Sharfi & Rosenblum, 2016). Implicated executive functioning also increases the likelihood that patients will use maladaptive coping strategies that reinforce dysfunctional behaviors and beliefs, which in turn leads to increased levels of stress, depressive symptoms and reduced quality of life (Brod et al., 2005). This interdependency between stress, immune activation, chronic pain, and depression-generated maladaptive coping techniques only exacerbates IBS symptoms and makes the problem severe over time.

Personality and IBS

Ever since Hippocrates proposed his theory of "four humors", there have been continuous attempts to attribute diseases to certain personality types (Block, 2002). Personality refers to individual differences in characteristic patterns of thinking, feeling and acting. Being relatively stable throughout individual's lifetime (Allemand et al., 2013; Costa Jr & McCrae, 1997; Robert & Paul, 1994; Vaidya et al., 2002) it can influence a person's attitudes, behaviors and stress resilience (Gerald et al., 2017; Jaksic et al., 2012;

Umbarger, 2014). It can affect pain duration and severity (Drossman, 1999; Gustin et al., 2016; Tanum & Malt, 2001; Zarbo et al., 2019), as well as the extent of functional impairment in different diseases. In addition to having effect on the disease, personality may have an effect to how patients respond to treatment. For example, the vulnerable type, characterized by lower extraversion, agreeableness, and conscientiousness and higher neuroticism, has been shown to be associated with a poorer outcome of treatment response compared to the resilient type (Kim et al., 2016).

One of the first studies to explicitly analyze the effect of personality on bowel movement was conducted in 1981, providing evidence that personality factors may be as important as dietary variables in determining stool production (Tucker et al., 1981). The study revealed significant differences among participants (n=85) in stool output even when dietary factors were held constant: heavier stools were produced by persons who were more socially outgoing, more energetic and optimistic and less anxious.

The NEO five-factor personality inventory is a widely accepted model for assessing personality across diverse cultures, viewing personality traits in terms of five basic dimensions (Costa Jr & McCrae, 1997). These dimensions are extraversion (talkativeness, assertiveness, activity; vs silence, passivity and reserve); agreeableness (kindness, trust, and warmth vs selfishness and distrust); conscientiousness (organization, thoroughness, and reliability vs carelessness, negligence and unreliability); neuroticism (nervousness, moodiness, temperamentality vs emotional stability); and openness to experience (imagination, curiosity, and creativity vs shallowness and imperceptiveness).

Most of the research that have looked into the role of personality in IBS focused on Big Five assessments and constructs such as alexithymia, characterized by reduced ability to identify, describe and discern subjective emotions and feelings, and distressed Type D personality, characterized by negative affectivity and social inhibition (Muscatello et al.,

2016). Although both alexithymia and type D personality constructs are highly relevant to the IBS population, for the purposes of the current paper, using data from Bergen Brain-Gut-Microbiota project, I will explicitly focus on the Big Five inventory.

There is a consistency across multiple studies showing that high neuroticism (Farnam et al., 2008; Farnam et al., 2007; Mousavinasab et al., 2007; Palmer et al., 1974; Tayama et al., 2012; Zarpour & Besharat, 2011) is a personality trait associated with IBS. In a Finnish study including 56 patients with FGIDs, the NEO-PI showed that both female and male patients had significantly higher levels of neuroticism than controls (Tanum & Malt, 2001). There are, however, more to it when it comes to nuances in the IBS patient types: some studies report higher scores for neuroticism in IBS-C patients compared to the other IBS patient groups (Farnam et al., 2007), while in other studies the IBS-D patients are found among the ones with the highest scores on this scale (Tayama et al., 2012).

Another personality trait relevant to IBS patients is conscientiousness. The findings here are conflicting. Thus, in some studies the score for conscientiousness is significantly lower in IBS patients compared to controls (Zarpour & Besharat, 2011). However, there are studies that report the opposite pattern – with higher scores for conscientiousness in the IBS group vs healthy controls (Farnam et al., 2007). Overall, there is obviously a call for more studies including personality among the wide range of measures needed to understand symptoms and treatment effects in patients with IBS.

Treatment strategies

The main strategies for treatment of patients with IBS are dietary approaches, microbial therapies, pharmacotherapy and psychotherapy (Camilleri, 2021).

Dietary Approaches

Many IBS patients report that certain foods trigger and/or worsen their IBS symptoms (Böhn et al., 2013; Simrén et al., 2001). A diet specifically developed for the management of

IBS is the low Fermentable Oligosaccharides, Disaccharides, Monosaccharides, And Polyols (FODMAP) diet. FODMAP is a collective term for short-chain carbohydrates that are incompletely absorbed in the small intestine, and includes oligosaccharides including fructans/fructo-oligosaccharides, and galacto-oligosaccharides, lactose, fructose in excess of glucose, and polyols such as sorbitol and mannitol (Whelan et al., 2018). When FODMAPs are fermented in the colon, they cause production of gas and increased luminal distention in the lower GI tract. While healthy individuals are not affected by it, IBS patients experience abdominal pain, flatulence, bloating and diarrhea after ingesting FODMAPs (Ong et al., 2010).

Recent meta-analyses have demonstrated beneficial effects of low FODMAP diet on IBS symptom severity scores and quality of life scores compared to the standard IBS diet recommended by NICE guidelines (Marsh et al., 2016; Varjú et al., 2017). However, due to its highly restrictive nature, adhering to the low FODMAP diet may be difficult for some patients. And despite the inherent limitations of the studies, risks of biases and in some cases, short duration (Rao et al., 2015; Zhan et al., 2017), low FODMAP still has the greatest evidence for efficacy in IBS among available dietary intervention studies (Dionne et al., 2018).

Microbial Therapies

Microbial therapies target gut microbiota which is dysregulated in IBS patients. Potential approaches include probiotics, synbiotics and fecal microbial transplants (Camilleri, 2021). Probiotics are living microorganisms which commonly comprises gut-friendly bacteria, sometimes also yeast, and are ingested in the form of supplements and probiotic-rich foods (Chong et al., 2019). Prebiotics are defined as non-viable food components that improve host gut health. Synbiotics refer to the combination of probiotics and prebiotics in food ingredients or supplements in a form of synergism (Chong et al., 2019).

The probiotic *Biofidobacterium* and *Lactobacillus* strains have been demonstrated to improve IBS symptoms (Guyonnet et al., 2007) and were shown to be superior to placebos in reducing IBS pain (Ford et al., 2014). *Bifidobacterium longum* NCC3001 was shown to reduce depression scores, improve quality of life, and reduce activity in the brain areas associated with negative emotional stimuli in patients with IBS (Pinto-Sanchez et al., 2017). In some trials, synbiotics have also shown to reduce IBS symptoms and bowel habits (Basturk et al., 2020; Colecchia et al., 2006), while another study showed no change in IBS symptom severity score, although there was an improvement in the inflammatory profile of the patients (Abbas et al., 2014).

Fecal microbial transplantation (FMT), a procedure that involves the transfer of intestinal microbiota from one individual to another (Cryan et al., 2019) is a new mode of IBS treatment with promising therapeutic effects. The results from a recent Norwegian RCT by El-Salhy et al. demonstrated a dose response reduction in IBS symptoms at 3 months after FMT – defined as a decrease of 50 or more points in total IBS symptom score, as well as reduction in the dysbiosis index and change in the intestinal bacterial profile (El-Salhy et al., 2020). These effects were accompanied by significant improvements in fatigue and the quality of life in patients who received FMT. Utilizing a well-defined donor with a normal DI and favorable specific microbial signature is essential for successful FMT.

Pharmacotherapy

Psychopharmacological treatment does not only address anxiety and depression in IBS patients, but may also have a direct effect on gut function. Antidepressant medications are therefore used to treat abdominal pain (typically using tricyclic antidepressants to treat diarrhea and selective serotonin reuptake inhibitors to treat constipation), and serotonin type 3 (5-HT3) antagonists are indicated for women with severe IBS-D lasting more than 6 months and for whom conventional therapy was inadequate (Camilleri, 2021). A network meta-

analysis showed that 5-HT3 antagonists are the most effective agents for the treatment of functional diarrhea and IBS-D (Black et al., 2020). Several approaches are available to treat constipation, including osmotic laxatives, chloride secretagogues, ion channel blockers and prokinetic agents (Camilleri, 2021).

Psychotherapy

When it comes to psychological therapies and their effect on IBS symptoms, the evidence is mixed (Camilleri, 2021). One systematic review and meta-analysis (Ford et al., 2019) reported that overall, the IBS symptoms did not improve in 52.2% of IBS patients receiving psychological therapies compared to 75.9% of IBS patients in the control condition receiving symptom monitoring, physician's "usual management", supportive therapy, or placebo. When all psychological therapies, including hypnotherapy, were considered the NNT was 4. CBT, relaxation therapy, multicomponent psychological therapy, hypnotherapy, and dynamic psychotherapy were all more effective than control therapy. Self-administered or minimal contact CBT, stress management, mindfulness meditation training, and CBT delivered via the internet were of no benefit.

Another review and meta-analysis included a wide range of RCT studies on psychotherapeutic interventions, including cognitive behavioral therapy (CBT), interpersonal psychotherapy (IPP), hypnotherapy and relaxation techniques (Zijdenbos et al., 2009). The results showed that CBT was better than usual care or waiting list for improving symptoms and quality of life for IBS patients at three months, but the results were not superior to placebo. Interpersonal psychotherapy was better than usual care or waiting list for adequate relief, symptom score and quality of life at 3 months. Relaxation or stress management proved to be better than usual care or waiting list for improving symptoms, abdominal pain and quality of life at 2 months. It should be noted that placebo response in IBS trials is very high,

ranging from 0 to 84% (Spiller, 1999) and in therapeutic trials it is not possible to completely separate the effect of the actual intervention from the placebo effect.

In addition to psychotherapeutic interventions, there is a broad evidence base for hypnotherapy as effective treatment of IBS (Krouwel et al., 2018; Lee et al., 2014; Schaefert et al., 2014). The most well-known technique have been termed gut-directed hypnotherapy (GDH) that teaches patients the necessary hypnotic skills, such as hand warmth on the abdomen and imagery to control gut function and reduce symptoms (Gonsalkorale, 2006).

The mechanisms by which psychological therapies might alleviate IBS symptoms point to various pathways that can be related to the earlier described biopsychosocial model (Drossman, 2016). IBS symptoms can be alleviated by reducing anxiety provoking behaviors, unhelpful ways of responding to stress and other techniques that help reduce the strain on HPA axis. Adaptive emotion regulation strategies and coping might also be beneficial in the light of this model.

Aims of the Study

The overall aim of this thesis is to acquire better understanding of associations between severity of IBS related pain, personality traits, cognitive and emotional function, and by this contributing to ideas for how to select and, hopefully, widen the treatment options for patients with IBS. The thesis will therefore include an empirical study of patients with IBS and controls related to this topic. Based on previous studies, patients with IBS are expected to report higher level of emotional symptoms (i.e., anxiety and depression), negative affectivity/neuroticism and conscientiousness, and lower level of cognitive function than controls. Based on Kennedy's model (Kennedy et al., 2012) emotional and cognitive functions and levels of chronic pain in the IBS patients are expected to be closely correlated. In particular, Kennedy's model considers three converging factors each implicated in both IBS and cognitive dysfunction: stress, immune activation and chronic pain. This model is not

restricted to patients with IBS, but it is expected that cognitive dysfunction observed in IBS may overlap with other disorders of the gut-brain axis, ranging from anxiety and depression to chronic fatigue and fibromyalgia (Kennedy et al., 2012).

Methods

This study is part of a larger ongoing project, the Bergen Brain-Gut project (BBG). Using a multidisciplinary approach, the BBG aims to increase knowledge and understanding of IBS and explore treatment strategies related to diet. This will be obtained by identifying structural and functional brain connectivity signatures and GI motility patterns, assess emotional function and cognitive function in multiple cognitive domains, analyze microbiota and biomarker data, and define phenotypes using a data-driven approach within a machine learning framework. One of the goals of the BBG project was to recruit patients for the FODMAP dietary intervention. This has put some restrictions on inclusion and exclusion criteria. Details on study procedure, inclusion and exclusion criteria and events during case–control characterization (baseline) and the following 12-week strict low-FODMAP diet intervention can be found in the study protocol presented by Berentsen et al. (Berentsen et al., 2020).

Patients

The current study includes data collected at baseline before January 2021. The included patients were between 18 and 65 years, and they fulfil Rome-III criteria for IBS. A total of 53 IBS patients and 34 healthy controls (HC) were included, 22 with IBS-D diagnosis, 22 with IBS-M, and 9 with an IBS-C diagnosis. The number of participants included in the data analyses varied, depending on the availability of data for the selected measures. For the purity of data analysis, no techniques for overcoming or compensating for lost or missing data were used. The number of included patients will be reported in the text or tables presenting results from the different measures.

Measurements

Irritable Bowel Syndrome – Symptom Severity Score (IBS-SSS)

IBS-SSS is a validated and standardized questionnaire used to assess the severity of IBS-symptoms (Francis et al., 1997). The form consists of five questions concerning severity of abdominal pain, frequency of abdominal pain, severity of distension, satisfaction with bowel habits and the symptoms' interference on the patient's life in its entirety. The severity of the symptoms is categorized based on the total score, into mild (75-175), moderate (175-300) and severe (>300), while a score less than 75 is considered to reflect that the patient is in remission. A reduction in the score by at least 50 points indicates a significant clinical improvement of the patient's IBS-like symptoms and is used to define successful effect of the low FODMAP intervention in the BBG study. In the present study, the total IBS-SSS is used to define severity of pain in patients with IBS (IBS pain) and healthy controls.

NEO Five-Factor Inventory-3 (NEO-FFI-3)

NEO-FFI-3 is a 60-item version of the NEO-PI-3 providing a quick and reliable measure of the Five-Factor model of personality (neuroticism, extraversion, openness, agreeableness, and conscientiousness). The instrument is well validated for use in several countries. Measures will include the 5 factors as well as profiles of factors for individual adults. In the BBG, the personality assessment is part of the phenotyping of adults with IBS and controls. In the present study, each of the five factors will be used both to characterize patients with IBS and HC, and to investigate their associations with IBS related pain.

Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)

The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) is a brief, individually administered test-battery designed as a screening instrument to evaluate neuropsychological status of adults, ages 20 to 89 years (Randolph et al., 2010). The test battery includes 12 subtests giving measures of attention, language,

visuospatial/constructional abilities, and immediate and delayed memory function according to available Scandinavian norms. In the present study, the results will be used to describe the cognitive function in the sample and to investigate associations with reports of IBS related pain.

Behavior Rating Inventory of Executive Function for Adults (BRIEF-A)

The Behavior Rating Inventory of Executive Function (BRIEF-A) is used to assess executive functions (EFs) as they are experienced in the home and work environments of the participants. The scale includes 86 items divided into 8 clinical scales (inhibit, shift, emotional control, initiate, working memory, plan/organize, organization of materials, monitor) and 2 validity scales (inconsistency and negativity). The eight scales form two broader indexes based on the factor structure, Behavioral Regulation and Metacognition, as well as an overall score, the Global Executive Composite (GEC) (Gioia et al., 2018).

Given the importance of the EF to behavior, the BRIEF family of instruments was designed for a broad range of individuals with developmental, neurological, psychiatric, and medical conditions. The BRIEF-A has been examined in clinical populations such as mild cognitive impairment, ADHD, epilepsy, traumatic brain injury, schizophrenia, and cancer survivors (Gioia et al., 2018). In the present study, the results will be used to assess executive functions in the sample and to investigate associations between IBS pain and executive function deficits, as well as associations between executive functions and personality measures.

Hospital Anxiety and Depression Scale (HADS)

HADS is a reliable self-assessment scale developed to detect symptoms indicating depression and anxiety in hospital medical outpatient clinic settings (Snaith & Zigmond, 1986). The anxiety and depressive subscales are also valid measures of severity of the emotional disorder. The questionnaire consists of 14 items, seven items assessing symptoms

of anxiety and seven items assessing symptoms of depression. The answer format of the items has four degrees scored with values 0 to 3. Anxiety and depression scores are obtained by simply summing up the scores of the seven items, yielding values between 0 and 21. The total HADS score is divided into three subgroups: 0-7 (non-cases), 8-10 (doubtful cases) and 11-21 (cases). These cut-offs (8+ and 11+) were defined on the basis of psychiatric ratings of anxiety and depression disorders. In the present study, the total HADS score and the anxiety and depression subscores were included to describe the emotional function in the IBS and the HC group.

Data Analysis

Exploratory data analyses were conducted using Python (https://www.python.org) and Jupyter notebooks (https://jupyter.org). More specifically, Pandas Numpy, Scikit-learn, Statsmodels and Penguin are used for statistical analysis and data processing. Matplotlib and Seaborn were used for data visualization. Data analysis has been conducted in Jupyter Notebooks, an open-source web application allowing to create and share documents that contain code, visualizations and narrative text explaining the obtained results. All code is stored on Github to support open science and reproducible research (https://github.com/irkyw/IBSpain-personality-cognition/blob/c199d48e9954523090f689314a32351f089491be/notebook.ipynb).

Python data visualization, including dataplots and heatmaps, are used to present data. The analyses are conducted in three steps. First, a set of independent sample t-test will be used to compare the IBS and HC groups on age and the selected measures of pain, emotional and cognitive function, and personality. Fisher's Exact test will be used to check if the proportion of men and women in each group were the same, and multiple comparisons were accounted for by reporting Bonferroni corrected p-values. One way ANOVA will be used to compare the IBS-M, IBS-D, IBS-C subgroups. Finally, a set of Pearson's correlation

coefficients will be computed to explore pairwise associations between IBS related pain measure and measures of age, emotional and cognitive function, and personality.

Results

Group Analyses

Age, IBS Pain and Anxiety/Depression Scores

There was no significant difference in gender distribution between the HC- and IBS group (Fisher exact test $p = .51$). The results from independent-samples t-test showed a significantly higher age in the IBS group (M =39.14, SD =10.72, $n = 50$) than the HC group (M = 30.65, SD =9.44, $n = 31$); $t(60) = 3.02$, $p = .04$, %95 CI [2.88, 14.11], $d = 0.82$. An independent-samples t-test showed significantly higher pain scores in the IBS (M = 261.88, SD = 82.22, $n = 42$) than the HC group (M = 35.36, SD = 33.82, $n = 25$); $t(65) = 13.1$, $p < .001$, %95 CI [191.99, 261.06], $d = 3.31$. An independent-samples t-test showed significant differences in both the subscores of anxiety and depression, and the total HADS score between the IBS and the HC groups (Table 2).

Table 2

Anxiety and Depression Scores in IBS patients and Healthy Controls

Variables	IBS group		Healthy Controls		*t*(65)	*p*	*Cohen's d*
	M	SD	M	SD			
Anxiety	8.29	4.31	3.84	3.12	4.50	<.001	1.14
Depression	5.17	3.12	2.04	2.32	4.34	<.001	1.10
HADS total score	13.45	6.37	5.88	5.10	5.05	<.001	1.28

Note. Mean parameter values are shown for IBS patients ($n = 42$) and HC ($n = 25$)

Cognitive Performance and Self-Reports of Executive Functions

The IBS group obtained significantly lower results than the HC group on the two memory indexes, immediate memory, and delayed memory (Table 3). With Bonferroni correction only delayed memory scale was left with a statistically significant value. No

significant differences were found for the visuospatial index and the verbal skills and attention indexes.

There were significant differences between the IBS and HC groups on several BRIEF-A measures (Table 4), including the shift, emotional control, initiate, working memory, organization of materials, as well as the two broader indexes, behavioral regulation, and GEC. With a Bonferroni correction, only the initiate and working memory subscales were left statistically significant. No significant differences were found for inhibit, self-monitor, plan organize and task monitor measures.

Table 3

RBANS Scores in IBS Patients vs Healthy Controls

Variables	IBS group		Healthy Controls		*t*(59)	*p*	*Cohen's d*
	M	SD	M	SD			
Immediate Memory	90.16	14.51	100.94	14.26	-2.66	.01	0.75
Visuospatial	94.90	12.05	94.22	13.02	0.20	.84	0.06
Verbal skills	96.48	14.52	98.11	12.88	-0.41	.68	0.12
Attention	94.74	10.66	99.00	17.08	-1.18	.34	0.33
Delayed Memory	93.51	13.59	108.06	15.82	-3.63	<.001	1.02

Note. Mean parameter values and t-test results for IBS patients (n = 43) and HC (n = 18)

Table 4

Group Differences in BRIEF-A Measures in IBS Patients vs Healthy Controls

Variables	IBS group		Healthy Controls		*t*(37)	*p*	*Cohen's d*
	M	SD	M	SD			
Shift	55.12	12.08	47.31	8.10	2.10	.043	0.71
Emotional C.	56.42	12.36	46.46	9.86	2.53	.015	0.86
Initiate	62.58	9.21	53.31	8.32	3.06	.004	1.04
WM	61.23	11.18	50.54	6.96	3.15	.003	1.07
Org. Materials	55.65	10.77	48.08	7.63	2.26	.029	0.77
Beh. Reg.	54.27	10.15	46.46	8.90	2.41	.02	0.82
Metacognition	60.50	9.38	51.38	7.35	3.06	.004	1.04
GEC	58.42	9.31	49.15	7.87	3.08	.004	1.05

Note. Mean parameter values and t-test results for IBS patients (n = 26) and HC (n = 13).

Emotional C. - Emotional Control, WM – Working Memory, Org. Materials – Organization of Materials, Beh. Reg. – Behavioral Regulation, GEC - Global Executive Composite

Personality Measures (NEO-FFI-3)

An independent-samples t-test was conducted to compare personality dimensions in the IBS and the HC group. Consistent with the primary hypothesis, there was a significant difference in Neuroticism scores (Table 5). The group differences were not statistically significant for any of the other personality dimensions.

Table 5

Group Differences in Personality Measures IBS Patients vs Healthy Controls

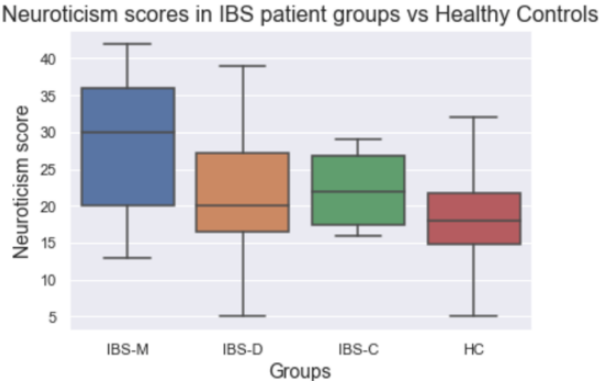
Variables	IBS group		Healthy Controls		*t*(51)	*p*	*Cohen's d*
	M	SD	M	SD			
Neuroticism	25.08	9.44	18.00	7.39	2.77	0.007	0.80
Extraversion	30.02	7.54	31.94	4.50	-0.98	0.32	0.28
Openness	26.45	8.02	30.66	8.55	-1.76	0.08	0.51
Altruism	31.45	6.71	31.27	4.73	0.10	0.91	0.02
Conscientiousness	31.94	6.50	31.38	5.95	0.30	0.76	0.087

Note: Mean parameter values and t-test results for IBS patients (n = 35) and HC (n = 18).

A one-way between subjects ANOVA showed a statistically significant effect of type of IBS diagnosis (IBS-C patients (n = 4), IBS-D (n = 14), IBS-M (n = 17) and HC (n = 18)) on the Neuroticism score [$F(3, 49) = 4.02$, $p = 0.01$]. None of the other NEO-PI scores were different between the two groups.

Figure 3

Neuroticism Scores in IBS Patient Groups vs Healthy Controls



Post hoc comparisons using the Tukey HSD test showed a statistically significant difference in Neuroticism score between the HC group (M = 18.00, SD = 7.39) and the IBS-M subgroup (M = 28.12, SD = 9.15); *meandiff* = 10.12, $p = .006$). No statistically significant differences were found between the IBS-D (M = 22.21, SD = 9.89) or IBS-C (M = 22.25, SD = 6.24) and HC.

Correlations between IBS Pain and Measures of Cognitive Function and Personality

Correlation matrixes with all pairwise correlations between pain and the other included measures are presented separately for the IBS (Figure A1) and the HC group (Figure A2). No significant correlations were found between IBS pain and age, but a moderate positive correlation was found between IBS pain and HADS total score, as well as between IBS pain and the HADS anxiety subscore in the IBS group (Table 6). When the results from the results from the IBS and HC groups were analyzed together, a strong positive correlation was found between the HADS total score and IBS pain $r(65) = .63$, $p < .001$, the HADS anxiety subscore and IBS pain $r(65) = .61$, $p < .001$, and a moderate positive correlation between the HADS depression subscale and IBS pain $r(65) = .52$, $p < .001$. The relationships between the HADS scores and the IBS pain measures are presented in Figure 4.

Table 6

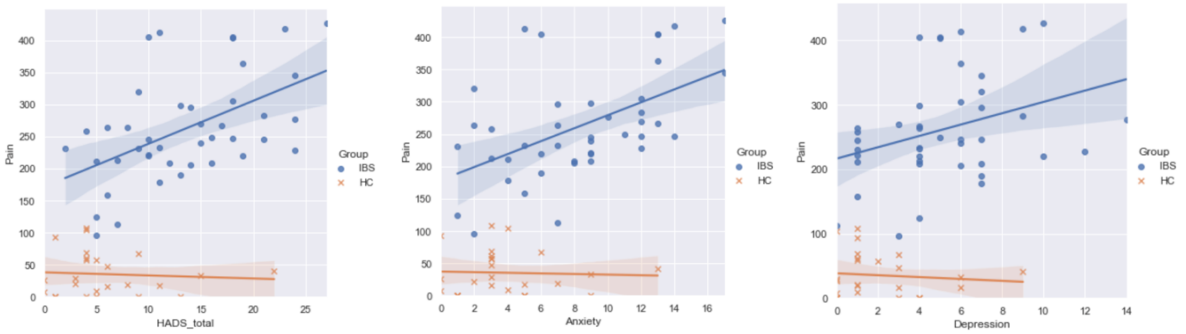
Correlations for HADS Scores and Pain in IBS group

Variable	M	SD	Pain	Anxiety	Depression	HADS total score
Pain	261.88	82.21	—			
Anxiety	8.28	4.30	0.53**	—		
Depression	5.16	3.12	0.33*	.45*	—	
HADS total score	13.45	6.37	0.51**	0.90**	0.80**	—

Note:
$^{*}p < .05$. $^{**}p < .001$. Correlations are presented for IBS group (n = 42).

Figure 4

Scatterplots – Anxiety and Depression vs Pain in IBS and HC groups

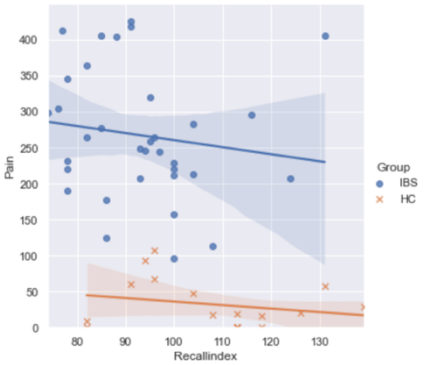


Pain and Measures of Cognitive Function in IBS group and Healthy Controls

For RBANS measures, when results from the IBS (n = 34) and HC (n = 17) groups were analysed together, a weak negative correlation was found between the immediate memory score and IBS pain $r(49) = -35.$, $p < .05$, while the correlation was moderate between IBS pain and the delayed memory score, $r(49) = -.44$, $p < .05$. With Bonferroni correction only the correlation between delayed memory score and IBS pain remains statistically significant $r(49) = -.44$, $p = .001$ (Figure 4). None of the other correlations between RBANS scores and the IBS pain score were statistically significant. During the partitioned analysis, no significant correlations were found between RBANS scores and IBS pain in the IBS group.

Figure 4

Scatterplot – Delayed Memory vs Pain in IBS and HC groups

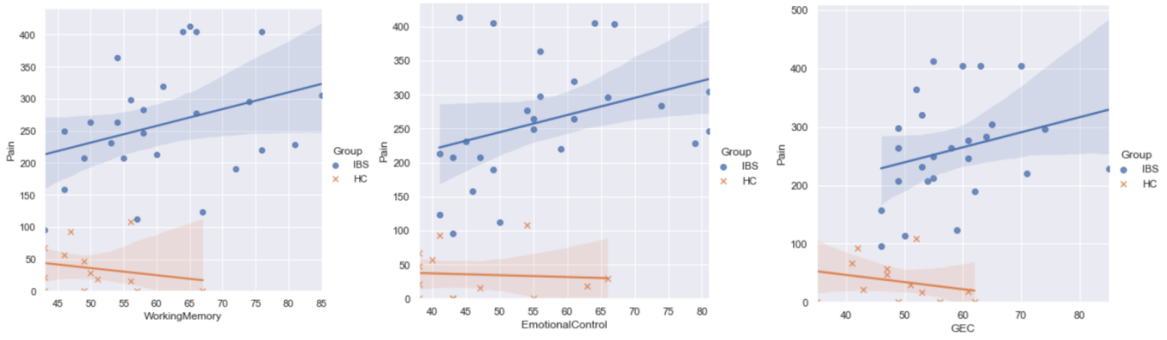


For BRIEF-A measures, when the results from the IBS (n = 26) and HC groups (n = 13) were analysed together, the following BRIEF measures were found to be moderately positively correlated with the pain score: the shift, $r(37) = .41$, $p = .008$, emotional control, $r(37) = .46$, $p = .003$, initiate, $r(37) = .40$, $p = .011$, working memory, $r(37) = .51$, $p = .0008$, behavioural regulation, $r(37) = .39$, $p = .01$, metacognition, $r(37) = .42$, $p = .009$ and the GEC, $r(37) = .45$, $p = .003$ scores. *A w*eak positive correlation was found between IBS pain and the Organisation of Materials score, $r(37) = .34$, $p = .04$.

With Bonferroni correction only emotional control, $r(37) = .46$, $p = .003$, working memory, $r(37) = .51$, $p = .0008$ and the GEC, $r(37) = .45$, $p = .003$ scores remained statistically significant (**Figure** 6). During partitioned analysis of the IBS group, no significant correlations were found between BRIEFA scores and the IBS pain score.

Figure 6

Working Memory, Emotional Control and GEC score vs Pain in IBS and HC groups



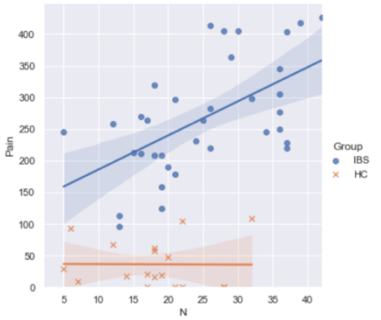
Pain and NEOPI Scores in IBS Group and Healthy Controls

The aggregated analysis, including results from both the IBS ($n = 35$) and HC ($n = 18$) groups, neuroticism and IBS pain scores were positively correlated at a moderate level, $r(51) = .55$, $p < .001$, while *e*xtraversion and IBS pain were found to be weakly negatively correlated $r(51) = -.28$, $p < .05$. With Bonferroni correction, only neuroticism was significantly correlated with pain, $r(51) = .55$, $p < .001$.

For IBS patients only, the neuroticism and IBS pain scores were positively correlated at a moderate level $r(33) = .57$, $p < .001$. Extraversion and IBS pain were found to be weakly negatively correlated $r(33) = -.33$, $p < .05$. With Bonferroni correction only neuroticism was significantly correlated with IBS pain at a moderate level, $r(33) = .57$, $p < .001$ (Figure 7). No statistically significant results were found for openness, altruism, and conscientiousness dimensions.

Figure 7

Scatterplot – Neuroticism vs Pain in IBS and HC groups



Discussion

The results of this study confirm the initial study hypothesis that IBS patients report significantly higher scores on a symptom scale assessing anxiety and depression, as well as lower level of cognitive function than healthy controls. The latter was shown on tests of immediate memory and delayed memory from RBANS and on the initiate and working memory subscales from BRIEF-A. Regarding personality, the results confirmed the hypothesis that IBS patients report higher level of negative affectivity/neuroticism than controls, while the assumption that IBS patients are likely to have higher conscientiousness was not confirmed. An analysis of the IBS subtypes suggested that IBS patients with high neuroticism are more likely to have an IBS-M diagnosis than any of the two other diagnostic subgroups. Correlation analyses only partially confirmed that IBS related pain are correlated with cognition, emotional function, and neuroticism.

For the aggregated analysis, i.e. when the correlation analysis included results from both the HC and IBS groups, a moderately positive correlations were found between IBS pain scores and the scores indicating reduced delayed memory function, mental flexibility (shift) and emotional control, reduced ability to initiate a task and working memory function. These results were also reflected in the aggregated scores from BRIEF-A (Behavioral Regulation and GEC). With Bonferroni correction, only the delayed memory score and the working memory, emotional control and the GEC scores remained statistically significant. For partitioned data analysis, in IBS group only, no significant correlations were found between any of the cognitive measures and the IBS pain score.

A first comment should be devoted to differences in the results between aggregated and partitioned data. These differences can be viewed as an example of what is referred to as Simpson's reversal paradox, which poses a dilemma of choosing which data should we trust – the aggregated or partitioned? Pearl (Pearl, 2000) argues that it depends on the data, and that the aggregated not the partitioned data should in many cases be used as the choice of action. In this study, there are arguments for sticking to the aggregated data, and use correlations from these analyses to understand the relationship between pain levels and reduced cognitive performance in IBS patients. This is related to the fact that it will not give any iatrogenic effects – the upside of using this information about associations between cognitive function and pain can be useful when we design treatments for this patient group. However, if we fail to account for the possibility that IBS patients have reduced performance in some cognitive measures, we may face the risk of developing treatments that will not suit this patient group. To achieve a more distinct answer to this, to understand how exactly cognitive measures correlate with pain in the IBS patients, studies with a larger sample are warranted.

On some measures, there were, however, similar results in both aggregated (for IBS and HC together) and partitioned (IBS only) analyses even in this small sample: moderate

positive correlations between IBS pain and the total and anxiety HADS scores, as well as significant positive correlations between neuroticism and the IBS pain score. Thus, the results are consistent with the existing literature on the assessment of cognitive deficits in chronic pain. This is true for impaired working memory, which is common in patients with chronic pain (Berryman et al., 2013; Dick & Rashiq, 2007). Problems due to poor ability to independently generate ideas, responses, or problem-solving strategies without external prompting (as measured by Initiate scale) are also consistent with previous studies including patients with chronic pain (Akira & Naomi, 2012; Berryman et al., 2014; Miyake et al., 2000). Likewise, increased neuroticism/negative affectivity, as well as problems with emotional regulation are also consistent with existing evidence for emotion dysregulation and negative emotionality in chronic pain (Baker et al., 2016; Bushnell et al., 2013; Shackman et al., 2011).

The results of the study are also consistent with the existing research on links between neuroticism and IBS symptoms, as well as neuroticism and chronic pain in general. Most of such research has focused on neuroticism as a causal or moderating factor. Some studies suggest that neuroticism is causally related to chronic pain because it involves stronger physiological response to stress (Breslau et al., 1996; Lahey, 2009; Pietri-Taleb et al., 1994). Other studies suggest that neuroticism is a moderator of pain experience, affecting adjustment to acute pain, and potentially contributing to the development of chronic pain(Asghari & Nicholas, 1999). However, there is a body of evidence showing that prolonged pain it itself can be a factor inducing personality and neurological changes (Gustin et al., 2014; Zoppi et al., 1984), as it may increase negative affectivity, as well as influence one's perception of agency to handle challenging events (Janssen, 2002).

Understanding the relationship between chronic pain, increased negative affectivity and cognitive functions is highly relevant for IBS patients. This is important for many

reasons: a) it will help us better understand the challenges faced by IBS patients in their daily life, b) this can be valuable information that would help us make psychotherapeutic interventions tailored to patients in this specific group. Chronic pain, experienced by IBS patients, may lead to substantial changes in the brain (Siddall, 2013), including changes in gray matter density of the frontal regions such as dorsolateral prefrontal cortex, which is vital for executive functioning (Apkarian et al., 2004). Likewise, the neurobiological findings on neuroticism show that people with high neuroticism have heightened reactivity in emotion-generating structures, such as increased insula activation and amygdala hyperexcitability, and decreased activity in prefrontal cortex (Keightley et al., 2003; Stein et al., 2007).

For IBS patients suffering from chronic pain, this means that in addition to higher levels of depression and anxiety symptoms and higher level of pain-induced negative emotion, they may have fewer mental resources to regulate their emotions and may have problems related to reduced mental flexibility. The key implications of reduced mental flexibility is a disadvantage in being able to move freely from one situation, activity, or from one aspect of a problem to another according to situational demands, being less likely to tolerate change, less flexible in problem solving or rigid when it comes to changing focus from one mindset to another (Gioia et al., 2018).

Similar to the therapeutic interventions used for treating and managing chronic pain in general, the majority of psychological interventions designed for IBS patients (cognitive-behavioral therapies and mindfulness-based therapies) normally require a certain level of attention control, mental flexibility and executive functioning in general. The findings of the effect of CBT on IBS symptom severity are inconsistent (Ford et al., 2019), some studies even show very weak effects of CBT on improving pain on pain in general (Williams et al., 2012). One possible explanation of such weak effects can be the heterogeneity of the ISB patients and differences in their cognitive functioning. Could it be the case that the “CBT pill” is

simply too hard to swallow by some of the IBS patients? If chronic pain induces maladaptive neurological changes and leads to such cognitive deficits as emotion dysregulation and other cognitive impairments, wouldn't it be too ambitious to treat IBS patients with therapies requiring exactly these cognitive capabilities to induce change?

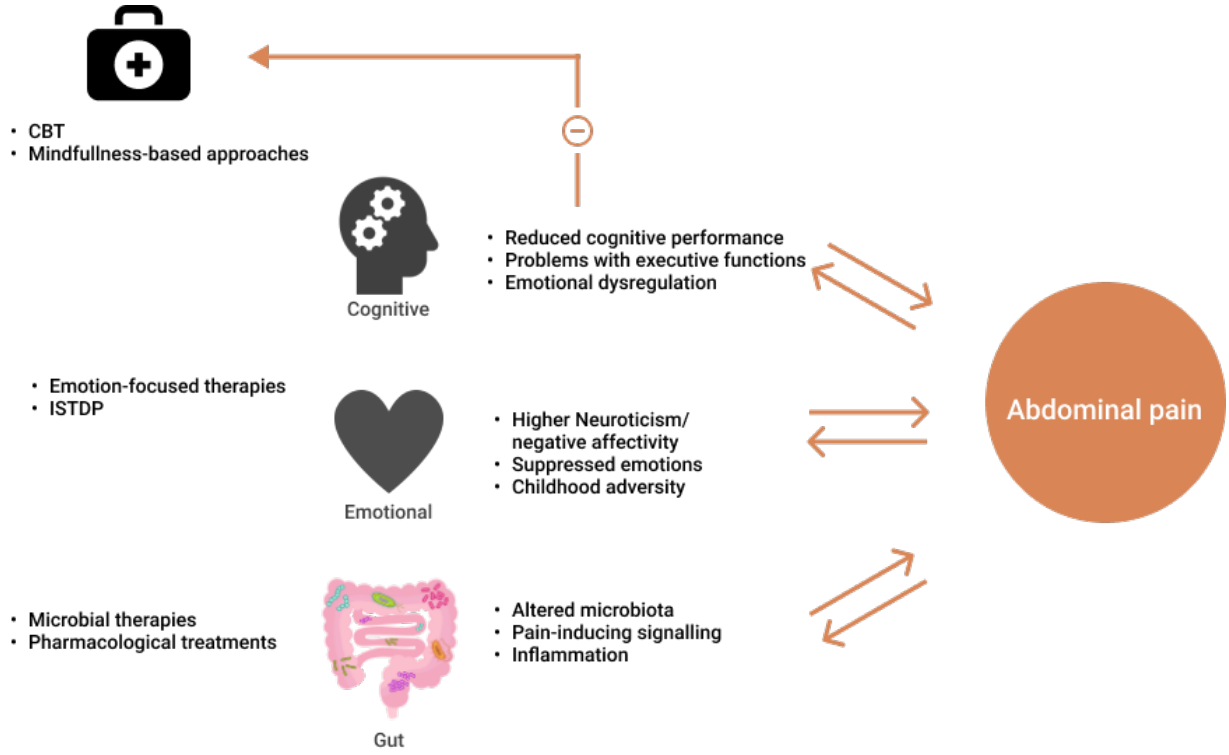
Given these finding, there might be a need to adjust psychotherapeutic approaches to treating IBS so that they a) account for the problems in executive functions typical for this patient group b) target the underlying neuroticism/negative affectivity that accompanies the disorder/chronic pain condition. Unfortunately for the patients, the higher the level of pain that they experience, the less cognitive capacity is left to benefit from interventions that rely entirely on patients' ability to self-reflect, reframe and analyze their cognitive schemas and behavior.

One of the more direct ways to alleviate pain, at least for a subgroup of IBS patients, is to directly target emotional processing, without too much reliance on cognitive capacity. For this, we can turn our eye to existing treatments that target negative affectivity and neuroticism, as well as existing research on the psychological processes relevant to pain. Neuroticism-oriented treatments, such as Unified Protocol for Transdiagnostic Treatment of Emotional Disorders (Barlow, 2010; Barlow et al., 2010) and a special neuroticism-oriented type of mindfulness-based cognitive therapy (MBCT) (Segal, 2002), focus on at extinguishing distress in response to experiencing of strong negative emotions (Sauer-Zavala et al., 2017; Sherman & Ehrenreich-May, 2020). These psychotherapeutic interventions, with their focus on stress reactivity, HPA axis and unhelpful ways of responding to stress, have shown promising results in reducing neuroticism and negative affectivity (Armstrong & Rimes, 2016). Other emotion-oriented interventions have demonstrated promising results in reducing chronic pain: expressing negative emotions (Pennebaker, 1997), as well as emotional experiencing proved beneficial for different types of pain (Kingston et al., 2007; Morone et

al., 2008; Wicksell et al., 2009). It has been also found that the increases in acceptance were correlated with symptoms improvement (McCracken et al., 2005; Vowles & McCracken, 2008).

Figure 8

Abdominal Pain, Related Variables and Treatment Strategies



Note. The picture of the gut from "Gut Microbiota" by Wakana Sasaki (https://doi.org/10.7875/togopic.2020.154). Copyright 2020 by DataBase Center for Life Science (DBCLS)

If we apply the results from the current research on psychotherapeutic interventions that reduce both neuroticism and experience of pain, most of them tend to converge on psychological processes behind adaptive emotional processing: emotional awareness, expression and experiencing, tolerating negative emotions, and accepting emotions as they are. We can also learn from ISTDP paradigm, with their focus on uncovering suppressed

emotions. Given the fact that there is a higher prevalence of adverse childhood experiences in IBS population, trauma screening and trauma-focused treatments may be also be warranted.

Advantages of the Study

Although there is a relatively large body of research on the relationship between neuroticism and IBS, the current study contributes to the existing literature by analysing not only personality of the IBS patients, but doing so in relation to cognitive and emotional function and levels of pain in individual patients. By this, we should have improved our understanding of how we best can use information about neuroticism, memory problems and capacity for idea generation/mental flexibility to widen the options for psychotherapeutic treatments that are accommodated to the personality, emotional and cognitive function of individual patients with IBS.

Limitations of the Study

Due to stringent requirements during the recruitment process of the Bergen Brain-Gut project, as well as multiple delays caused by the covid-19 pandemic, the data analysis was conducted before data collection was completed, resulting in a marginally low number of participants (n = 52). This was for example a factor that gave varying results when building logistic regression/linear regression models within a machine learning framework. The study is therefore limited to explorative analytic methods.

Conclusion

The data from this study suggest that cognitive and emotional function and aspects of personality are important to understand the primary symptom of IBS patients: abdominal/visceral pain. Out of the many variables associated with pain, neuroticism/negative affectivity, memory problems and reduced emotional regulation seem essential to understand problems related to patients with IBS. These temperamental and cognitive characteristics, as well as information about how chronic pain may induce long term structural and functional

brain changes, are probably crucial when it comes psychotherapeutic interventions designed to alleviate pain. To be more specific, I suggest that existing treatment should account for the underlying negative emotionality in patients with high scores on neuroticism, as well as use strategies that adapt the demand on cognitive function to individual patients.

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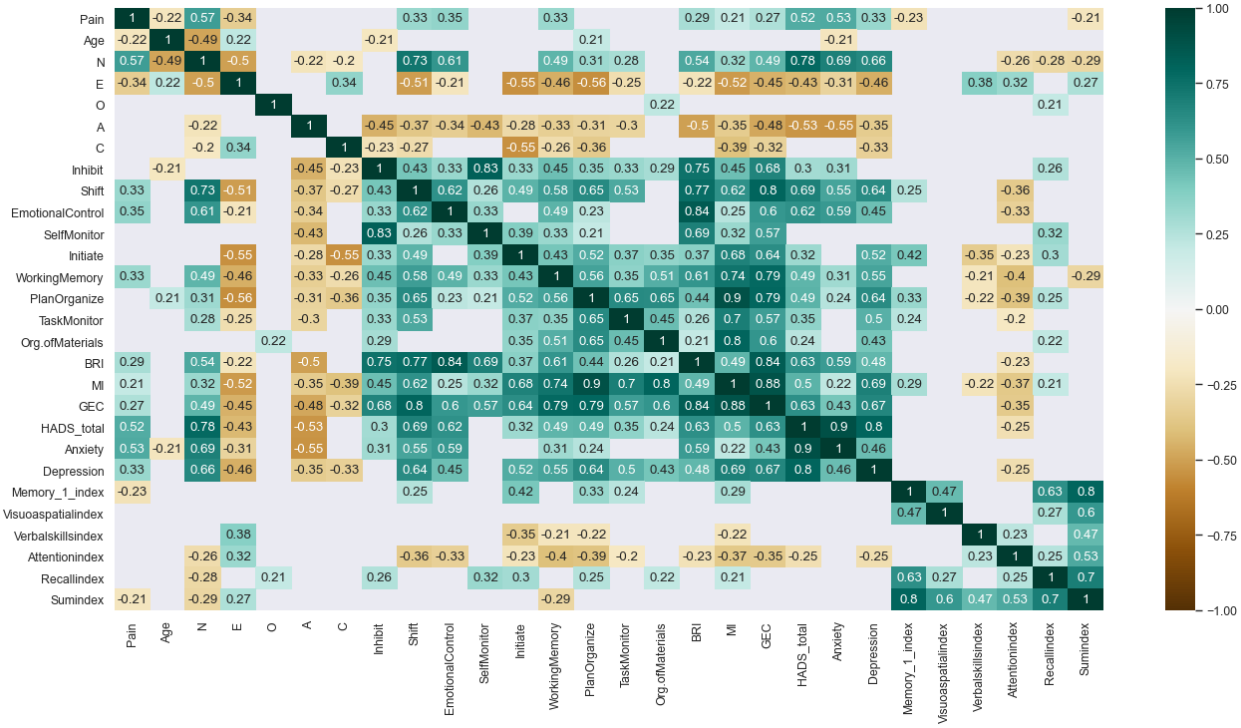
Appendix A

Figure A1

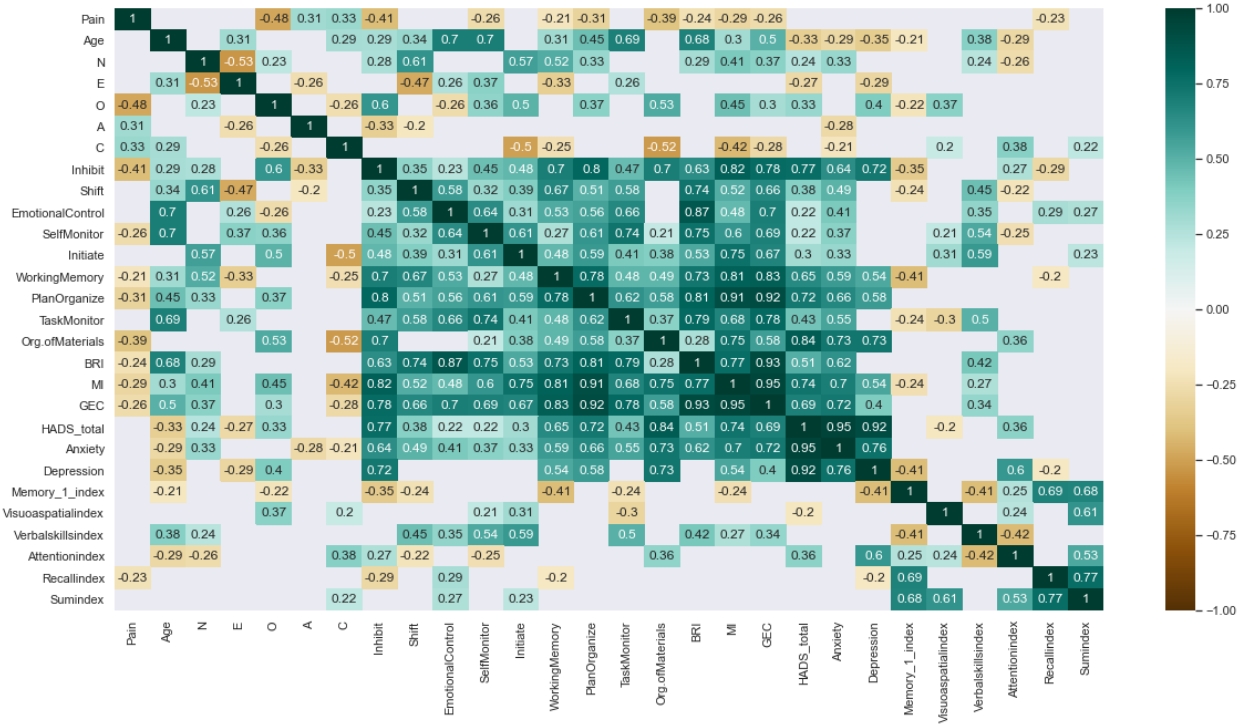
Correlation matrix – pain and measures of cognitive function and personality – IBS group



Note: N – Neuroticism, E – Extraversion, O – Openness, A – Altruism, C – Conscientiousness, , Org.Materials – Organization of Materials, BRI – Behavioural Regulation Index, MI – Metacognition, GEC - Global Executive Composite, HADS – Hospital Anxiety and Depression Scale, Memory_1_index – Immediate Memory, Recallindex– Delayed Memory, Sumindex – total RBANS score

Figure A2

Correlation matrix – pain and measures of cognitive function and personality – HC group



Note: N – Neuroticism, E – Extraversion, O – Openness, A – Altruism, C – Conscientiousness, , Org.Materials – Organization of Materials, BRI – Behavioural Regulation Index, MI – Metacognition, GEC - Global Executive Composite, HADS – Hospital Anxiety and Depression Scale, Memory_1_index – Immediate Memory, Recallindex– Delayed Memory, Sumindex – total RBANS score.