Virtual Reality: A New Treatment Paradigm for Disorders of Gut-Brain Interaction?

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Abstract: Disorders of gut-brain interaction (DGBIs), previously called functional bowel disorders, are prevalent, reduce patients' quality of life, and impose a significant negative economic impact on the health care system. Functional dyspepsia and irritable bowel syndrome (IBS) are 2 of the most common DGBIs. An overlying, and in many cases unifying, symptom for many of these disorders is the presence of abdominal pain. Chronic abdominal pain can be difficult to treat, as many antinociceptive agents are associated with side effects that limit their use and other agents may only partially improve, but not completely relieve, all aspects of the pain. Novel therapies to alleviate chronic pain and the other symptoms that characterize DGBIs are thus needed. Virtual reality (VR), a technology that immerses patients in a multisensory experience, has been shown to relieve pain in burn victims and other instances of somatic pain. Two recent novel studies have demonstrated that VR has the potential to play an important role in the treatment of functional dyspepsia and IBS. This article examines the development of VR, its role in the treatment of somatic and visceral pain, and its potential position in the treatment of DGBIs.

Keywords
Abdominal pain, dyspepsia, functional dyspepsia, irritable bowel syndrome, virtual reality

Disorders of gut-brain interaction (DGBIs), previously called functional bowel disorders, include functional dyspepsia (FD), irritable bowel syndrome (IBS), and centrally mediated abdominal pain syndrome, among other disorders.[1] These disorders can be defined using the Rome IV criteria for both clinical purposes and research studies.[1,2] FD is the most prevalent DGBI, affecting approximately 10% of the US population.[3] The global prevalence of IBS is nearly as common, with an estimated 4% to 9% of the general population being affected.[4] DGBIs have a significant negative financial impact on the health care system and dramatically reduce patient quality of life (QoL).[5,6]

Effectively treating symptoms of DGBIs to improve overall patient health and well-being is important but can be difficult for a number of reasons. One, there is no validated treatment algorithm for either FD or IBS.[7-9] Two, despite the prevalence of FD, no medication is approved by the US Food and Drug Administration for its treatment. Three, not

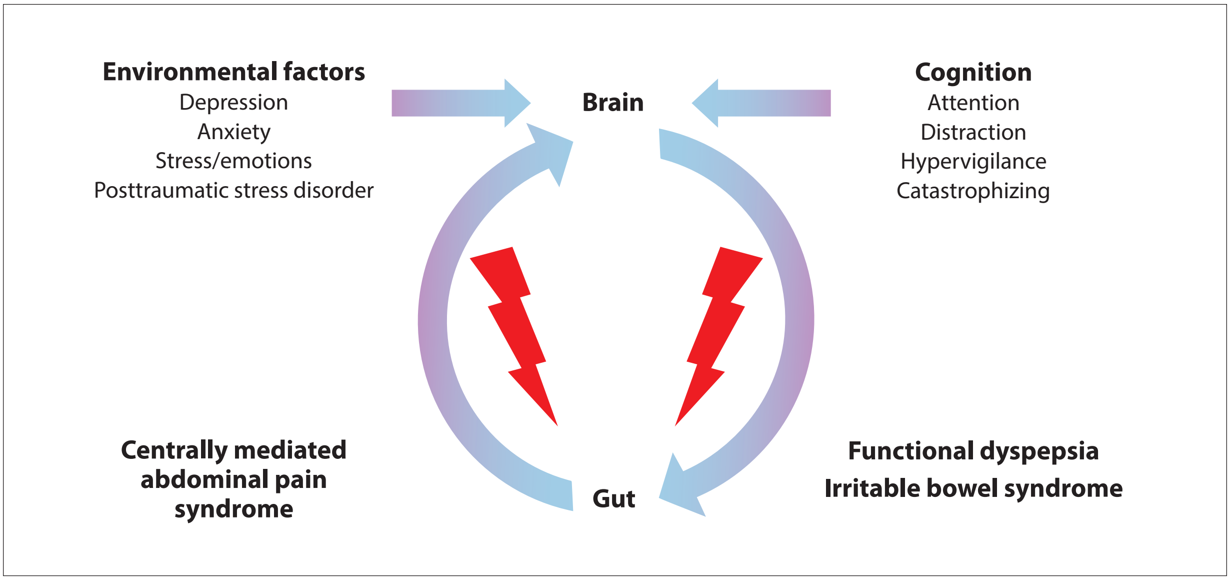

Figure 1. The bidirectional brain-gut axis plays a critical role in disorders of gut-brain interaction. Environmental factors (eg, stress/emotions) can affect the brain, which then affects the gastrointestinal tract via descending pathways. Gastrointestinal disruption (eg, inflammation, changes in the gut microbiome, medications, ischemia) leading to the development of irritable bowel syndrome, functional dyspepsia, or centrally mediated abdominal pain syndrome can stimulate pain receptors and affect central nervous system function via ascending pathways.

every intervention works in every patient, even when the reported symptoms appear identical. Although 8 medications are currently approved for the treatment of IBS, these agents do not always resolve the cardinal symptom of IBS—abdominal pain.[9] Four, medications used to treat visceral pain frequently cause side effects (eg, fatigue, constipation, nausea, urinary retention). Thus, the management of abdominal pain in patients with DGBIs can be difficult.

The precise mechanisms underlying the development of abdominal pain in patients with FD and IBS are unknown, although a number of theories exist regarding predisposing factors (eg, genetics, environmental issues, history of abuse, inflammation, medications) and perpetuating factors (eg, ongoing inflammation, changes in the gut microbiome, psychological factors).[2,7,8] Extensive research has demonstrated that most patients with FD and IBS have a component of visceral hypersensitivity to account for their symptoms.[2,7,8] Persistent abdominal pain in patients with FD and IBS also represents, in part, changes to the central nervous system (CNS). Mechanistically, changes in CNS function develop because persistent abdominal pain, transmitted through ascending pain pathways, modifies CNS physiology and structure.[10-12] These CNS changes are important to understand when discussing potential therapies for FD and IBS, as medications that target only the gastrointestinal (GI) tract may not be able to effectively influence the multiple complex ascending and descending pain pathways that characterize the brain-gut axis (Figure 1). In these patients, using a second agent that targets the CNS and/or descending pathways may help achieve a maximal reduction in abdominal pain.[13] Neuromodulators are often used to treat persistent symptoms of abdominal pain secondary to a DGBI; however, these agents may cause side effects in some patients and are not always widely accepted by patients or providers owing to connotations that symptoms are solely because of underlying anxiety or depression.[14,15] A readily available, safe, easy-to-use, and effective therapy that improves or eliminates DGBI symptoms, especially abdominal pain, would prove invaluable. Virtual reality (VR) may be a vital treatment for the central (ie, CNS) component of abdominal pain. This article examines the development of VR, its role in the treatment of somatic and visceral pain, and its potential position in the treatment of DGBIs.

What Is Virtual Reality?

VR is a computer-generated depiction of a 3-dimensional (3D) environment that makes patients feel as if they are part of a virtual environment. Motion trackers built into the device measure the position of the head and adjust the visual image accordingly. This enables the user to engage in environments that appear and feel similar to real-world objects, views, and events. Headphones provide sounds that further engross the patient into the virtual world. VR is unlike other audiovisual technologies in its ability to generate meaningful and positive emotional experiences.[16] The effect of VR is mediated through several psychological mechanisms, most notably *presence*, which is the ability of VR to convey a strong sense of *just being there*, wherever *there* happens to be.[17,18] For example, VR can simulate relaxing on a beach, meditating on a mountain top, flying over nature scenes, or swimming with dolphins, among countless other natural and fantastical environments. When used in the appropriate way, at the appropriate time, and with the appropriate patient, these virtual journeys may be able to impact clinical outcomes.

The History of Virtual Reality

VR has changed dramatically since it was first developed over 60 years ago. In 1961, 2 Philco Corporation engineers created the first head-mounted display (HMD), called Headsight. The device used 2 video screens, 1 for each eye, and incorporated a magnetic tracking device. The first HMD connected to a computer was invented by Harvard Professor Ivan Sutherland and his student Bob Sproull in 1968 and was so heavy that it was nicknamed the Sword of Damocles, as it had to be suspended from the ceiling. The term *virtual reality* was first coined in 1987 by Jaron Lanier, who founded the Visual Programming Lab. In the past decade, technological advances have seen the advent of lightweight headsets that provide a 3D immersive experience complete with sound and even the ability to monitor patients' physiologic responses such as heart rate and eye movement.

How Does Virtual Reality Work?

The precise mechanism for how VR works is not fully elucidated, and its effects vary based upon the underlying disease state, the chronicity and intensity of the disorder, and the psychological profile of the patient. To date, research indicates that VR reduces acute pain through several proposed psychological effects. First, by stimulating the visual cortex while engaging other senses, VR is thought to act as a distraction to limit the user's perception of painful stimuli.[19] The result is a form of inattentional blindness, in which the prefrontal cortex redirects attentional bandwidth to the virtual environment, leaving diminished ability to attend to pain signals outside the spotlight of attention.[20] By overwhelming the visual, auditory, and proprioception senses, VR is thought to create an immersive distraction that restricts the brain from processing pain in the short term. Second, VR creates an illusion of time acceleration, effectively shortening the perception of pain episodes through its effects on prefrontal time perception.[21-23] For example, controlled trials reveal that VR reduces the perceived length of labor and delivery during childbirth, episiotomy repair, endoscopic procedures, and chemotherapy infusions by an average of 30% to 50%.[21-23] These effects have been demonstrated both clinically and experimentally. For example, Hoffman and colleagues revealed that VR affects pain processing in the sensory and insular cortex, suggesting that it can reduce both the intensity of pain and the emotional response to pain.[24,25] Moreover, the investigators found that VR has the same functional magnetic resonance imaging (fMRI) effects as hydromorphone, and was equally effective at blocking acute pain as the powerful opioid.[24] Clinical trials also demonstrate reductions in sensory, cognitive, and affective components of pain, suggesting that the fMRI changes shown experimentally appear to translate into improved patient-centered outcomes across multiple dimensions of pain. Third, VR offers an immersive platform through which patients can acquire and begin to master specific self-regulation skills and cultivate adaptive cognitive patterns that reduce pain processing.[26,27] These mechanisms are synergistic with distraction, enhancing both the effectiveness and durability of the intervention. In chronic pain, adaptive cognitive regulation (including reduced pain catastrophizing) has been shown to reduce pain intensity, emotional distress, and hypervigilance for pain, and to favorably alter both the function and structure of the brain such that future pain is diminished.[26,27] Studies of VR that support the development of adaptive skills and cognitive functions in phobia,[28-34] anxiety,[35-37] and depression[38,39] suggest that skills learned and practiced in VR are durable.

Virtual Reality for the Treatment of Experimental Pain

One of the first studies to evaluate the benefits of VR involved a thermal pain stimulus. The investigators hypothesized that a more immersive VR experience using a wider field-of-view device would reduce symptoms of experimental thermal pain more than a limited field-of-view VR device. In this prospective study, 77 undergraduate volunteers (ages 18-23 years) were exposed to thermal pain and randomized to either a high-tech VR device (large field of view) or a low-tech device (limited field of view).[40] The authors reported that the volunteers randomized to the high-tech device had a greater reduction in pain unpleasantness and worst pain, compared with those randomized to the low-tech device. In a model of experimental pain using a cold pressor challenge, Dahlquist and colleagues evaluated the benefits of interactive (more immersive) VR compared with video game distraction in 41 healthy children (ages 6-14 years).[41] Each subject acted as his or her own control. The authors reported that both distraction conditions improved pain tolerance, although there was a significantly greater response using the VR program in children older than age 10 years. Although the methodologies of these 2 studies differed on several key levels (eg, age of patients, experimental pain stimulus, duration of stimulus intensity), both studies demonstrated that an immersive VR experience was capable of reducing somatic pain. However, because experimental pain is briefer and usually milder than other painful chronic conditions, the generalizability of these studies to the treatment of DGBIs is unclear.

Virtual Reality for the Treatment of Somatic Pain

Two studies evaluated the utility of VR at reducing discomfort associated with port access. Both were performed in pediatric oncology patients.[42,43] Neither study showed a significant improvement in pain related to port access. However, it is important to note that neither protocol used immersive VR that typifies current products; the studies used distraction with a joystick or remote control. As well, both studies involved only a single, brief experience, which may not provide adequate time for VR to work.

Changing dressings for burn victims can be painful. Two studies have evaluated the utility of VR for relieving dressing changes in burn victims. The first study assessed 11 burn victims (ages 4-40 years) who required inpatient care for their injuries.[44] The investigators focused on a 6-minute period of debridement thought to be most painful. This 6-minute period was then divided into two 3-minute segments. Patients were randomized to receive VR for a 3-minute segment at either the start of the most painful debridement process or at the end. Although the sample size was small, the investigators reported that patients who used VR during a 3-minute debridement period had less pain than those who did not use VR. The second study involved a large group of children (N=42; ages 3-14 years).[45] In this study, augmented VR (in which a virtual image was projected onto the real world) was compared with standard of care. In contrast to the study by Hoffman and colleagues,[44] the investigators reported that augmented VR was not useful at reducing pain in patients with short dressing changes (30 minutes or less). However, for patients with longer dressing changes, augmented VR was useful. Of note, this type of VR is quite different than the immersive VR now used in most research studies.

Two other studies evaluated the utility of VR for the treatment of pain in adolescent patients hospitalized for burns.[46,47] A study by Schmitt and colleagues involved a within-subject design (N=54; ages 6-19 years) with each patient serving as his or her own control.[46] Sessions lasted 30 to 40 minutes over 1 to 5 days. VR was shown to be an effective analgesic in combination with physical therapy, with patients reporting a 27% to 44% reduction in pain (P<.05). In a slightly smaller study of 41 adolescent patients (ages 11-17 years), a randomized, parallel-group study design was used to compare VR with standard distraction (watching television) for the treatment of burn pain.[47] Interestingly, this study did not show a difference in pain as reported by the patients, although nursing staff reported a statistically significant reduction in pain related to dressing changes. These discordant results highlight the need for large prospective studies using standardized immersive VR protocols and validated questionnaires to assess pain response.

Hospitalized patients frequently report pain; one study reported that one-quarter of hospitalized patients experienced pain self-rated as unbearable.[48] Pain in hospitalized patients is typically treated with pharmacologic agents. However, VR has the potential to reduce pain without the side effects that accompany many antinociceptive agents (eg, sedation, confusion, constipation, urinary retention, nausea). To evaluate the efficacy and safety of VR in the hospitalized setting, Tashjian and colleagues performed a prospective cohort study of 100 hospitalized patients (mean age 50 years) randomly assigned to a 1-time 3D VR intervention vs a 2-dimensional (2D) distraction video (observation of a televised nature video).[49] Each intervention, performed at bedside, lasted 15 minutes. Using an 11-point numeric rating scale, the investigators found that the immersive 3D VR program reduced pain more than the 2D program (65% vs 40%; P=.01) with a number needed to treat of 4 patients. No adverse events were reported.

Complex regional pain syndrome (CRPS), which may develop after trauma to an extremity, can be a debilitating disorder for many patients and resistant to standard antinociceptive therapy. Mirror visual feedback (MVF) therapy is used in some centers to treat CRPS. In a small open-label trial combining VR with MVF, 4 of 5 adult patients (mean age 56 years) with CRPS reported a 50% reduction in limb pain using VR-MVF therapy once a week for 5 to 8 sessions.[50] No side effects were reported. Larger prospective studies using a sham-VR comparator are needed to confirm these findings.

Virtual Reality for the Treatment of Disorders of Gut-Brain Interaction

DGBIs are characterized by abnormalities in the brain-gut axis, the complex bidirectional pathway of nerves connecting the GI tract to the brain, and vice versa. Critical to the understanding of this bidirectional highway

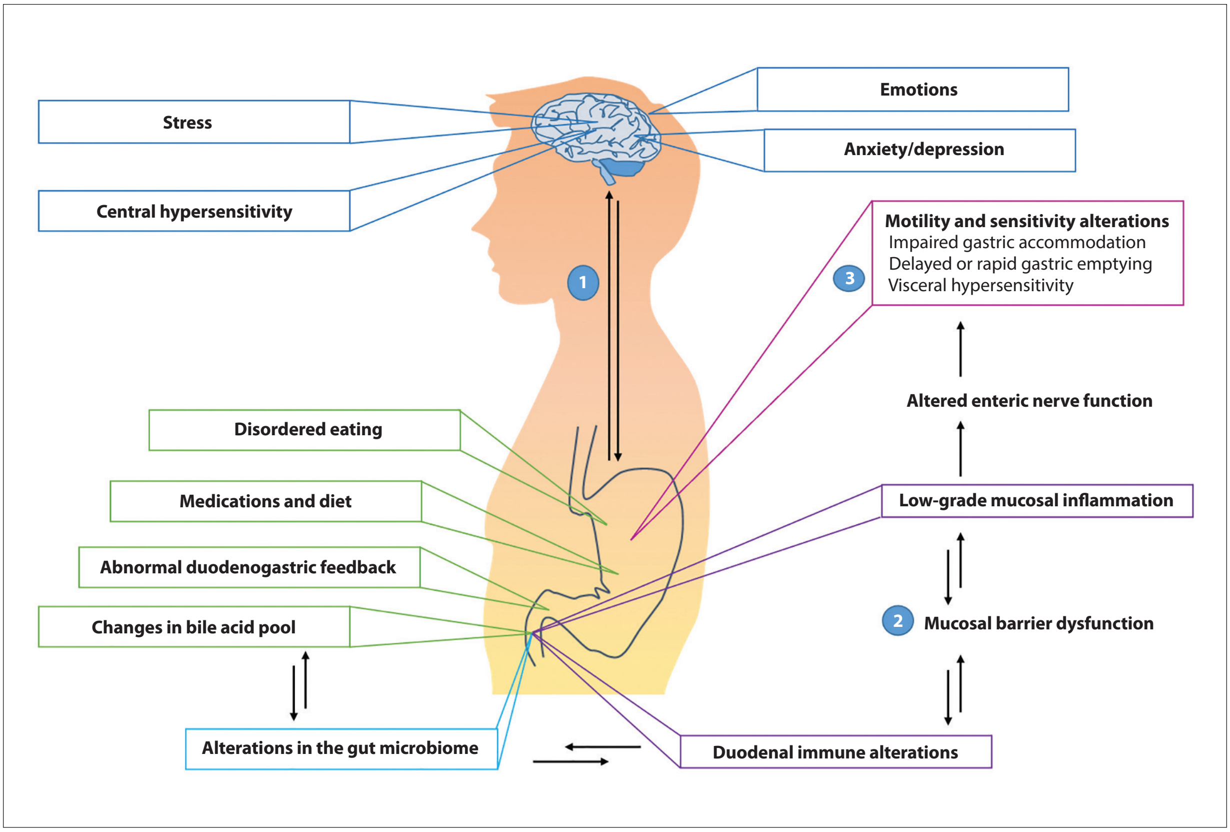

Figure 2. Pathophysiologic processes influence the development of functional dyspepsia (FD), a disorder of gut-brain interaction (1). FD is a heterogenous disorder with regard to both symptoms and underlying pathophysiology. A variety of processes and insults can lead to the development of FD symptoms. For example, duodenal inflammation from medications or an infection may lead to changes in intestinal permeability that can then lead to recruitment of inflammatory cells with release of cytokines adjacent to sensory neurons, thereby causing pain (2). Alternatively, impaired gastric accommodation, rapid gastric emptying (3), dietary factors, changes in the gut microbiome or bile acids, and duodenal sensitivity to acid, among other factors, may all play a role in the generation of FD symptoms.

and its role in DGBIs is an awareness of the complex relationship of pain processing regions and emotional and cognitive centers within the CNS. Multiple studies have demonstrated that environmental factors (eg, emotions, stress, anxiety, depression, poor sleep, medications) can affect brain function, which subsequently influences GI tract function.[14,51] Similarly, alterations in gut function caused by changes in the gut microbiome, microscopic inflammation, medications, or other reasons can modulate pain transmission at the dorsal horn of the spinal cord, influence ascending spinal cord pathways, and thus change CNS function. Therapies directed at pain pathways and emotional centers in the brain (eg, cognitive behavioral therapy [CBT], hypnotherapy) improve IBS symptoms.[7-9] Not surprisingly then, VR, which influences CNS function, should be able to lessen symptoms of DGBIs. Patients with DGBIs with coexisting anxiety and depression may note a lessening of those symptoms as well, based upon several small studies using VR with reduction in psychological distress as an endpoint.[52,53]

Virtual Reality for the Treatment of Functional Dyspepsia

Abdominal pain, sometimes characterized more specifically by patients as epigastric pain, pressure, and/or fullness, is a typical symptom of FD. Other common symptoms include early satiety, bloating, nausea, and vomiting.[7,54] The Rome IV criteria can be used to categorize FD into 2 broad symptom-based subgroups: epigastric pain syndrome and postprandial distress syndrome (PDS) (Table 1).[54] Distinguishing these 2 subgroups enables clinicians to focus on the predominant and/or most bothersome FD symptom and thereby potentially guide individualized therapy. A number of pathophysiologic processes contribute to the development of FD (eg,

Table 1. Rome IV Classification of Functional Dyspepsia With Subtypes

Symptom onset ≥6 months earlier
Symptoms should be active within the past 3 months
One or more of the following symptoms: • Bothersome postprandial fullness • Bothersome early satiation • Bothersome epigastric pain • Bothersome epigastric burning
No evidence of structural disease likely to explain the symptoms (ie, normal upper endoscopy)
Epigastric pain syndrome subtype: Must include 1 or both of the following symptoms ≥1 day per week: • Bothersome epigastric pain (ie, severe enough to impact usual activities) • Bothersome epigastric burning (ie, severe enough to impact usual activities)
Postprandial distress syndrome subtype: Must include 1 or both of the following symptoms ≥3 days per week: • Bothersome postprandial fullness (ie, severe enough to impact usual activities) • Bothersome early satiation (ie, severe enough to prevent finishing a regular-sized meal)

Modified from Stanghellini V et al.[54]

impaired gastric accommodation, rapid gastric emptying, delayed gastric emptying, increased sensitivity to chemicals or to stretch/distension of the stomach, abnormalities in intestinal permeability, changes in the gut microbiome); the end result for all patients, however, is the development of abdominal pain (Figure 2).[7,55] Clinicians use a host of interventions to treat symptoms of FD; however, most interventions have limited utility and no medication is approved by the US Food and Drug Administration or European Medicines Agency for the treatment of FD.[7] This landscape led to the first study evaluating the safety and efficacy of VR for the treatment of FD.

Cangemi and colleagues performed a prospective, single-center, randomized, controlled, double-blinded, pilot study of adult patients with FD (Rome IV criteria).[54,56] Enrolled patients were randomized in a 2:1 ratio (experimental:control), in which patients in the experimental group were given a VR headset with software consisting of immersive audiovisual programs, and patients in the control group were given an identical headset with 2D nature videos. Patients were asked to use their headset at least daily and completed the Patient Assessment of Gastrointestinal Disorders–Symptom Severity Index (PAGI-SYM) and Nepean Dyspepsia Index (NDI) questionnaires at their initial visit, after 1 week of use, and at the conclusion of the 2-week study. Thirty-seven patients were enrolled in the study (27 in the experimental group, 10 in the control group). Most patients were women (81%) and had PDS (54%); the mean age was 45 years. Patients used the VR headset an average of 1.3 times/day for a mean of 23.2 minutes/day. Although total PAGI-SYM scores significantly decreased for all patients, those in the experimental group had greater improvement in mean total PAGI-SYM scores (2.51 at baseline to 1.83 at week 2) compared with the control group (2.50 at baseline to 2.04 at week 2; P=.046). Furthermore, QoL significantly improved for all patients, as the total NDI QoL score increased from 40.97 (baseline) to 57.14 (week 2; P=0); however, patients in the experimental group saw greater improvement in QoL, compared with control patients. No serious adverse events were reported. The most commonly reported nonserious adverse effects were headache and dizziness; 1 patient in the experimental group withdrew because of migraines. Although only a pilot study of 2 weeks' duration, this randomized controlled trial (RCT) demonstrates that VR is safe to use in patients with FD and has the potential to improve FD symptoms and QoL. A longer study is clearly needed to verify these results. Figure 3 shows a conceptual model of how VR may improve FD symptoms. The theory is that VR will modulate brain activity via immersive distraction, which reduces pain signals from the brain to the gut (central downregulation; right side of Figure 3). A reduction in pain signals to the gut, and improvement in chronic visceral pain, should then reduce signals sent from the gut to the brain via ascending pain pathways (left side of Figure 3), leading to an overall improvement in symptoms.

In the context of reviewing VR for the treatment of FD, it is worth noting that 2 studies evaluated the efficacy of VR for the treatment of eating disorders. Both found that maladaptive eating behaviors were more likely to improve in the VR group compared with the CBT group or the relaxation training group.[57,58] As many dyspeptic symptoms are meal-related, and because some patients with FD develop secondary eating disorders, these findings support the theory that VR may play a vital role in treating meal-related FD symptoms.

Virtual Reality for the Treatment of Irritable Bowel Syndrome

IBS is a prevalent DGBI.[2,8,9,11,59] It is a heterogenous condition with complex underlying pathophysiology that varies from patient to patient (Table 2). Symptom expression represents, in part, visceral hypersensitivity.[2,8,9,11,29,59] Some patients with persistent abdominal pain have a component of central hypersensitivity as well. Eight

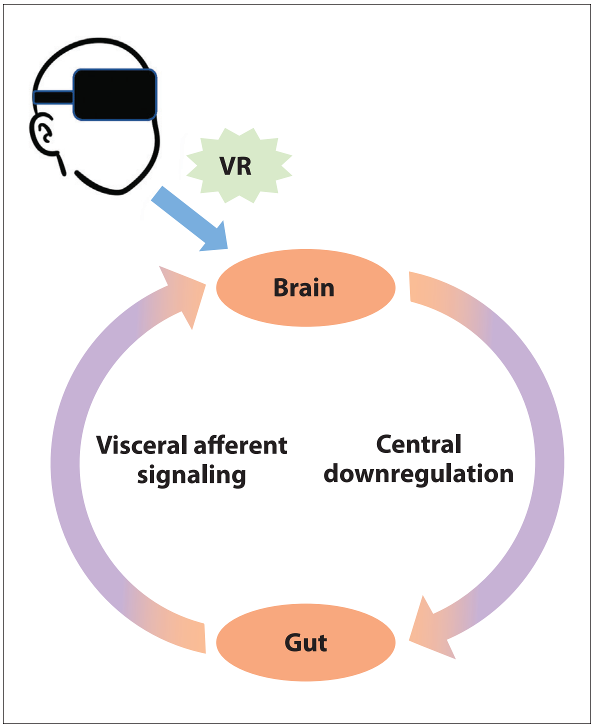

Figure 3. A conceptual model of virtual reality (VR) modulating gastrointestinal tract sensation is depicted. Recognizing the importance of the brain-gut axis, therapy directed centrally should theoretically improve gastrointestinal symptoms. Although the exact mechanism of action of VR is not known, distraction likely modulates descending pathways from the brain to the gut (central downregulation; right side of the figure), with subsequent reduction in stimulation of visceral pain receptors, thereby leading to a reduction in ascending pain signals (a reduction in visceral afferent signaling; left side of the figure).

medications are currently approved for the treatment of IBS: 5 for IBS with constipation predominance and 3 for IBS with diarrhea predominance.[9] Although these agents are effective at alleviating some IBS symptoms, many patients struggle with persistent abdominal pain. Therapies directed at the brain-gut axis in these patients, such as CBT and hypnotherapy, have proved beneficial. However, finding a therapist, and finding the right one, can be difficult; in addition, costs are not always covered by insurance.[9,59] Given its success in treating other chronic pain syndromes as previously discussed, VR appears to be a potentially useful therapy. Until recently, however, no studies had been performed in this area.

Spiegel and colleagues developed a specific VR program (IBS/VR) designed to treat patients with IBS.[60] A multidisciplinary team developed 4 virtual environments: an immersive experience about the brain-gut axis, an IBS-specific CBT module, a gut-directed meditative module, and a module addressing social isolation and stigma. Patients with IBS were exposed to the VR modules and then debriefed. Based upon patient interviews, software changes were made and then further interviews were performed in order to fine-tune the program. The end result was the development of a first-in-kind VR program for IBS patients of all subtypes. The next step, which is currently in the planning phase, is to test this IBS-specific VR program on a large group of patients prospectively.

Table 2. Rome IV Criteria for Irritable Bowel Syndrome

Symptom onset ≥6 months earlier
Symptoms should be active within the past 3 months
Recurrent abdominal pain ≥1 day per week (on average) in the past 3 months associated with ≥2 of the following: • Related to defecation • Associated with a change in frequency of stool • Associated with a change in form (appearance) of stool

Modified from Lacy BE et al.[2]

Virtual Reality for the Treatment of Other Gastrointestinal Disorders

The safety of VR and its many apparent benefits will likely lead to further studies in the GI arena. Chronic abdominal pain, not meeting criteria for either IBS or FD, is certainly an area of interest, especially in the current climate with fears of opioid abuse and overuse. Chronic nausea and vomiting could potentially respond to VR, as some patients develop nausea and vomiting owing to a conditioned response. Functional bloating, which can be very difficult to treat, is another area of interest. The availability of cheaper headsets will help stimulate the field; the ability to use scientifically validated programs designed specifically for DGBIs, such as IBS/VR, will be critical.

Conclusion: What Does the Future Hold?

Chronic abdominal pain, which characterizes many DGBIs, is a debilitating disorder for tens of millions of adult Americans. Medical therapy is ineffective for many patients or associated with multiple side effects. VR has the potential to alleviate chronic abdominal pain without the side effects associated with commonly used antinociceptive agents. Additionally, it should be noted that VR has been shown to be effective in treating psychological disorders such as anxiety and depression, which frequently coexist with DGBIs and exacerbate symptoms such as abdominal pain, seemingly making VR an attractive potential treatment modality for DGBIs. Furthermore, in an era when on-demand digital health applications are becoming increasingly sought after and utilized, VR offers the unique ability to deliver personalized, on-demand treatment in any setting, including home, office, and travel.

However, the field is still developing and future trials will need to be designed and conducted rigorously in order to obtain meaningful data on efficacy, safety, and durability of VR treatment. For example, VR programs will need to be designed and validated for specific patient populations. The IBS/VR program is a good example of a disease-targeted VR therapy developed in partnership with patients using human-centered design principles.[60] VR programs need to be immersive, should be used for appropriate periods of time, and should use validated questionnaires to assess pain perception and, in children, pain behavior (crying, grimacing, moaning). Once efficacy is established for a specific disease state (in sham-controlled trials), studies using VR as adjunctive therapy, as well as studies comparing VR with diet, medications, and psychological-based therapies (such as CBT), should all be performed to best understand the role of VR in the treatment algorithm for patients with DGBIs. Finally, from a commercial perspective, if VR RCTs show both efficacy and safety, headsets will need to be readily available at a reasonable price and ideally covered by insurance.

Disclosures

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