

Neuroscience of Virtual Reality: From Virtual Exposure to Embodied Medicine

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Abstract

Is virtual reality (VR) already a reality in behavioral health? To answer this question, a meta-review was conducted to assess the meta-analyses and systematic and narrative reviews published in this field in the last twenty-two months. Twenty-five different articles demonstrated the clinical potential of this technology in both the diagnosis and the treatment of mental health disorders: VR compares favorably to existing treatments in anxiety disorders, eating and weight disorders, and pain management, with long-term effects that generalize to the real world. But why is VR so effective? Here, the following answer is suggested: VR shares with the brain the same basic mechanism: embodied simulations. According to neuroscience, to regulate and control the body in the world effectively, the brain creates an embodied simulation of the body in the world used to represent and predict actions, concepts, and emotions. VR works in a similar way: the VR experience tries to predict the sensory consequences of an individual's movements, providing to him/her the same scene he/she will see in the real world. To achieve this, the VR system, like the brain, maintains a model (simulation) of the body and the space around it. If the presence in the body is the outcome of different embodied simulations, concepts are embodied simulations, and VR is an embodied technology, this suggests a new clinical approach discussed in this article: the possibility of altering the experience of the body and facilitating cognitive modeling/change by designing targeted virtual environments able to simulate both the external and the internal world/body.

Virtual Reality in Behavioral Health: A Meta-Review

THIS SPECIAL ISSUE presented and discussed different virtual reality (VR) applications for behavioral health. But is VR already a reality in behavioral health? To answer this question, a meta-review was conducted to assess the meta-analyses and systematic and narrative reviews (see Fig. 1 for the methodology) published in this field in the last 22 months.

Twenty-five different articles^{1–25} (see Table 1 for the articles' list and a summary of their conclusions) demonstrated the clinical potential of this technology in both the diagnosis and the treatment of mental health disorders. Nine articles^{1,2,6,9,14,15,19,18,22} reviewed the available literature on the effectiveness of VR in psychiatric/mental health treatment.

All of the articles suggest that VR is suitable for the treatment of mental health problems and could make an important

contribution in many different areas, from anxiety and eating disorders to psychosis and addiction.

The most common use of VR in behavioral health is for exposure therapy (VR exposure [VRE]). VRE is similar to classic exposure therapy^{10,16,26}—the patient is exposed to a graded exposure hierarchy—with the only difference being that VR is substituted for other exposure techniques (e.g., in vivo or imaginal exposure). In the treatment of complex anxiety disorders, the use of VRE is often combined with other techniques such as breathing or relaxation exercises,²⁷ attentional and autonomic control training,²⁸ biofeedback,^{29,30} and/or cognitive restructuring.³¹

Five articles,^{5,8,10} including a meta-analysis,^{11,16} specifically explored the use of VRE in the treatment of anxiety disorders. The available data show that VR is able to reduce anxiety symptoms significantly in different anxiety

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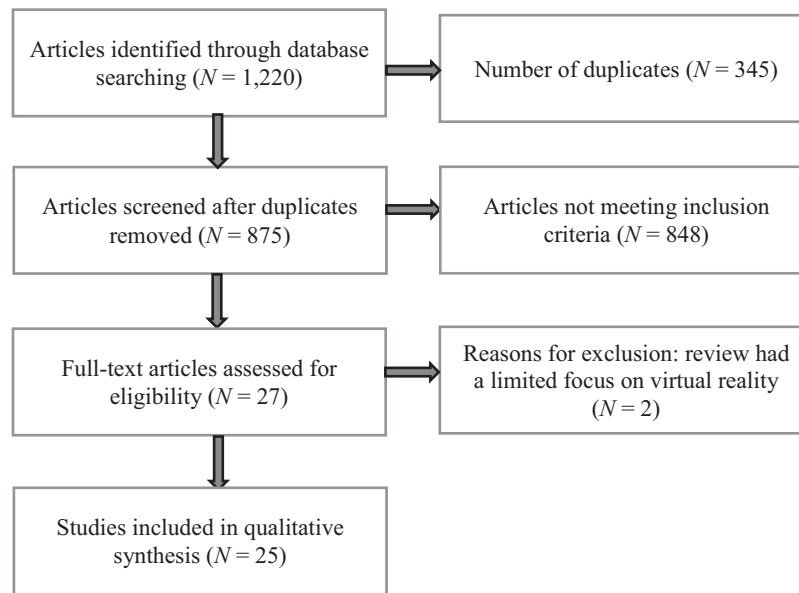


FIG. 1. Meta-review methodology. Using the Google Scholar and Scopus databases, a systematic search was conducted to identify reviews (both systematic and narrative) and meta-analyses that reported on the effects of virtual reality (VR) in the assessment and treatment in behavioral health: anxiety disorders, pain management, schizophrenia spectrum disorders, eating and weight disorders, autism spectrum disorders, personality disorders, and substance use disorders. Guidelines for conducting a systematic review discussed by Uman¹⁶² were followed. The “free-form” question was as follows: “Do virtual environments perform equal-to-or-better-than traditional modalities in behavioral health?” The outcome of interest was reviews and meta-analyses answering this question in any area of behavioral health. The following search terms were used: (“Virtual Reality” AND (“Review” OR “Meta-analysis” OR “metaanalysis”)) AND (“anxiety” OR “phobia” OR “fear” OR “stress” OR “pain” OR “schizophrenia” OR “psychosis” OR “obesity” OR “eating disorders” OR “bulimia” OR “binge eating” OR “anorexia”, OR “autism” OR “Asperger” OR “substance” OR “drug” OR “nicotine” OR “cocaine” OR “opioids”). The search targeted articles published between November 2, 2016, and August 1, 2018. Inclusion criteria included (a) reviews or meta-analyses, (b) English language journals, and (c) peer-reviewed journals. Exclusion criteria included (a) articles related to the use of VR in surgery or in physical and cognitive rehabilitation; and (b) articles lacking basic information about the selection of the discussed articles. The meta-review flow diagram is shown.

disorders: phobias,³² post-traumatic stress disorders,³³ panic disorder and agoraphobia,³⁴ social anxiety disorders,³⁵ psychological stress,³⁶ and generalized anxiety disorders.³⁷ The clinical outcome is generally superior to waitlist control conditions and comparable to in vivo exposure-based interventions.

A second group of five articles^{3,12,13,17,23} evaluated the efficacy of VR in the treatment of eating and weight disorders. In this field, VR is used in two different ways.³⁸ First, VR cue exposure to critical stimuli (e.g., food or human bodies) allows both a reduction in the level of anxiety elicited by them and disruption of the reconsolidation of negative memories.^{39,40} Second, VR is used to facilitate the update of existing body representations.^{41,42} According to a recent theory,^{43–47} eating and weight disorders may be the outcome of a broader impairment in multisensory body integration that locks the individuals to an old memory of the body.⁴⁸ In this view, even if the subject is able to lose weight after a diet, the multisensory impairment does not allow her/him to experience the new body and reduce the level of body dissatisfaction. VR allows a wrong representation of the body to be updated through two different strategies. In the first—“reference frame shifting”^{49,50}—the subject re-experiences in VR a negative situation related to the body (e.g., teasing) in both the first and third person (e.g., seeing and supporting her/his avatar in the VR world). In the second—

“body swapping”^{51,52}—VR is used to induce the illusory feeling of ownership of a virtual body with a different shape and/or size. Even if the number of available controlled studies is less than for anxiety disorders, the field has rapidly evolved.¹⁷ Specifically, four different randomized controlled trials—one with eating disorders,⁵³ one with morbid obesity,⁵⁴ one with binge-eating,⁵⁵ and one with binge-eating and bulimia⁵⁶—have shown after 6-month and 12-month follow-ups that VR had a higher efficacy than the gold standard in the field, that is, cognitive-behavioral therapy.

A third group of three articles^{20,21,24} analyzed the use of VR in pediatric psychology, with a specific focus on VR applications for the assessment of children suspected of having autism spectrum disorder⁵⁷ or other neurodevelopmental disorders^{58,59} (e.g., attention-deficit hyperactivity disorder). In this field, different from the previous ones, the level of clinical evidence available is still low, even if the existing data suggest moderate evidence about the effectiveness of VR-based treatments.²⁴ In relation to this topic, another article specifically explored the use of VR for the assessment of psychiatric disorders,⁴ finding that virtual worlds are able to induce and assess psychiatric symptoms simultaneously, with significant correlations between VR measures and traditional diagnostic tools. Moreover, VR is also effective in assessing cue reactivity⁶⁰: its use is able to increase subjective craving in smokers,^{61,62} alcohol drinkers,⁶³ eaters,⁶⁴ and cocaine-dependent individuals.⁶⁵

TABLE 1. META-ANALYSES AND SYSTEMATIC AND NARRATIVE REVIEWS PUBLISHED IN THE LAST 12 MONTHS RELATED TO THE USE OF VIRTUAL REALITY IN THE DIAGNOSIS AND TREATMENT OF MENTAL HEALTH DISORDERS

| <i>Review type</i> | <i>Article</i> | <i>Included studies</i> | <i>Conclusions (from the articles)</i> |
|--|--|---|---|
| Systematic meta-review | Riva G, Baños RM, Botella C, et al. Transforming experience: the potential of augmented reality and virtual reality for enhancing personal and clinical change. <i>Frontiers in Psychiatry</i> 2016; 7:164. ¹ | 27 systematic reviews and meta-analyses | “The available data support the use of this technology in the treatment of anxiety disorders, pain management, obesity and eating disorders, and stress-related disorders. But still, there is no clear good quality evidence for or against using VR for the treatment of depression and schizophrenia.” |
| Systematic review (mental health) | Freeman D, Reeve S, Robinson A, et al. Virtual reality in the assessment, understanding, and treatment of mental health disorders. <i>Psychological Medicine</i> 2017; 47:2393–2400. ² | 285 studies | “VR environments can elicit psychiatric symptoms, manipulation of VR can inform the understanding of disorders, and simpler psychological treatments can be successfully administered in VR. The most established finding is that VR exposure-based treatments can reduce anxiety disorders, but there are numerous research and treatment avenues of promise.” |
| Reply to the above systematic review (eating and weight disorders) | Riva G. Letter to the editor: virtual reality in the treatment of eating and weight disorders. <i>Psychological Medicine</i> 2017; 47:2567–2568. ³ | 3 studies | “Three different RCTs have shown at 1-year follow-up that VR for eating and weight disorders has a higher efficacy than the gold standard in the field, i.e. cognitive-behavioral therapy (CBT).” |
| Narrative review (mental health therapy) | Mishkind MC, Norr AM, Katz AC, et al. Review of virtual reality treatment in psychiatry: evidence versus current diffusion and use. <i>Current Psychiatry Reports</i> 2017; 19:80. ¹⁹ | Not reported | “More research is needed before VRE may be considered standard of care in some areas; however, for patients with PTSD or anxiety, and especially patients not responding or not willing to participate in traditional therapy, the use of VRE may be considered as an option. The use of VR for other conditions such as chronic pain, rehabilitation, and addictions also shows clinical promise.” |
| Systematic review (mental health assessment) | van Bennekom MJ, de Koning PP, Denys D. Virtual reality objectifies the diagnosis of psychiatric disorders: a literature review. <i>Frontiers in Psychiatry</i> 2017; 8:163. ⁴ | 39 studies | “Nearly all VR environments studied were able to simultaneously provoke and measure psychiatric symptoms. Furthermore, in 14 studies, significant correlations were found between VR measures and traditional diagnostic measures. Relatively small clinical sample sizes were used, impeding definite conclusions.” |
| Narrative review (anxiety disorders) | Lindner P, Milloff A, Hamilton W, et al. Creating state of the art, next-generation virtual reality exposure therapies for anxiety disorders using consumer hardware platforms: design considerations and future directions. <i>Cognitive Behaviour Therapy</i> 2017; 46:404–420. ⁵ | Not reported | “While having been researched for decades and proven efficacious for the treatment of anxiety disorders, the pending and ongoing release of consumer-targeted VR hardware platforms signals an opportune time to develop the next generation of VR exposure therapies for widespread dissemination as self-help applications and integration into regular health care settings.” |
| Systematic review (mental health) | Massetti T, Crocetta TB, Silva TDD, et al. Application and outcomes of therapy combining transcranial direct current stimulation and virtual reality: a systematic review. <i>Disability & Rehabilitation: Assistive Technology</i> 2017; 12:551–559. ⁶ | 11 studies | “The use of tDCS combined with VR showed positive results in both healthy and impaired patients including pain management. Future studies with larger sample sizes and homogeneous participants are required to confirm the benefits of tDCS and VR.” |

(continued)

TABLE 1. (CONTINUED)

| <i>Review type</i> | <i>Article</i> | <i>Included studies</i> | <i>Conclusions (from the articles)</i> |
|--|---|-------------------------|--|
| Systematic review (mental health) | Jordan SW, Grindle M, van Woerden HC, Kamel Boulos MN. Head-Mounted Virtual Reality and Mental Health: Critical Review of Current Research. JMIR Serious Games 2018; 6:e14. | 82 studies | “Our review demonstrated that VR is effective in provoking realistic reactions to feared stimuli, particularly for anxiety; moreover, it proved that the immersive nature of VR is an ideal fit for the management of pain. However, the lack of studies surrounding depression and stress highlight the literature gaps that still exist.” |
| Systematic review and meta-analysis (acrophobia) | Arroll B, Wallace HB, Mount V, et al. A systematic review and meta-analysis of treatments for acrophobia. Med J Aust 2017; 206:263–267. | 16 studies | “A range of therapies are effective for acrophobia in the short term but not in the long term. Many of the comparative studies showed equivalence between therapies, but this finding may be due to a type II statistical error. The quality of reporting was poor in most studies.” |
| Narrative review (psychosis) | Rus-Calafell M, Garety P, Sason E, et al. Virtual reality in the assessment and treatment of psychosis: a systematic review of its utility, acceptability and effectiveness. Psychological Medicine 2017 Jul 24 [Epub ahead of print]. ⁷ | 50 studies | “Virtual reality is a promising method to be used in the assessment of neurocognitive deficits and the study of relevant clinical symptoms. Furthermore, preliminary findings suggest that it can be applied to the delivery of cognitive rehabilitation, social skills training interventions and virtual reality-assisted therapies for psychosis.” |
| Systematic reviews (phobias) | Botella C, Fernández-Álvarez J, Guillén V, et al. Recent progress in virtual reality exposure therapy for phobias: a systematic review. Current Psychiatry Reports 2017; 19:42. ⁸ | 11 studies | “VRET applications have become an effective alternative that can equal the results of traditional treatments for phobias from an efficacy point of view. However, they are also tools capable of enhancing the psychological treatment field.” |
| Narrative review (anxiety disorders) | Maples-Keller JL, Yasinski C, Manjini N, et al. Virtual reality-enhanced extinction of phobias and post-traumatic stress. Neurotherapeutics 2017; 14:554–563. ¹⁰ | Not reported | “VRE is consistent with models of extinction learning and provides several advantages for use within exposure-based interventions. Broadly, extant research provides support for the effectiveness of VRE in reducing symptoms of specific phobias and PTSD, with outcomes generally superior to waitlist controls and comparable with traditional exposure therapy.” |
| Meta-analysis (flight anxiety) | Cardoş RAI, David OA, David, DO. Virtual reality exposure therapy in flight anxiety: a quantitative meta-analysis. Computers in Human Behavior 2017; 72:371–380. ¹¹ | 11 studies | “Results pointed out significant overall efficiency of VRET in flight anxiety at post-test and follow-up. Analysis highlighted the superiority of VRET vs. control conditions at post-test and follow-up and the superiority of VRET vs. classical evidence-based interventions at post-test and follow-up.” |
| Narrative review (weight disorders) | Castelnuovo G, Pietrabissa G, Manzoni GM, et al. Cognitive behavioral therapy to aid weight loss in obese patients: current perspectives. Psychology Research & Behavior Management 2017; 10:165–173. ¹² | Not reported | “Another current and future scenario where CBT could be improved in the management of obesity is represented by virtual reality (VR) applications, such as the VR-enhanced CBT that is a sort of enhanced CBT of obesity with a VR module focused on unlocking the negative memory of the body, changing its dysfunctional behavioral correlates, and managing negative emotional states.” |

(continued)

TABLE 1. (CONTINUED)

| <i>Review type</i> | <i>Article</i> | <i>Included studies</i> | <i>Conclusions (from the articles)</i> |
|---|---|-------------------------|--|
| Narrative review (weight disorders) | Paul L, Van Der Heiden C, Hoek HW. Cognitive behavioral therapy and predictors of weight loss in bariatric surgery patients. <i>Current Opinion in Psychiatry</i> 2017; 30:474–479. ¹³ | Not reported | “Although empirical evidence is still scarce, results show that CBT is effective in reducing disordered eating disorders and depression in bariatric patients. New techniques for applying CBR by virtual reality potentially make CBT more accessible and less costly.” |
| Systematic review (clinical medicine) | Dascal J, Reid M, Ishak WW, et al. Virtual reality and medical inpatients: a systematic review of randomized, controlled trials. <i>Innovations in Clinical Neuroscience</i> 2017; 14:14–21. ¹⁴ | 11 studies | “Data from 11 eligible studies provide insight into three current medical applications of VR technology: pain distraction, eating disorders, and cognitive/motor rehabilitation. Overall, a majority of studies from the past decade found VR to be efficacious, easy to use, safe, and contributing to high patient satisfaction.” |
| Systematic review and meta-analysis (procedural pain) | Chan E, Foster S, Sambell R, Leong P. Clinical efficacy of virtual reality for acute procedural pain management: A systematic review and meta-analysis. <i>PLoS ONE</i> 2018; 13:e0200987. | 20 studies | “VR may have a role in acutely painful procedures, however included studies were clinically and statistically heterogeneous. Further research is required to validate findings, establish cost efficacy and optimal clinical settings for usage. Future trials should report in accordance with established guidelines.” |
| Narrative review (clinical medicine) | Li L, Yu F, Shi D, et al. Application of virtual reality technology in clinical medicine. <i>American Journal of Translational Research</i> 2017; 9:3867–3880. ¹⁵ | Not reported | “VR has shown to be effective in reduction of burn-induced pain and management of pain in other situations ... Virtual reality exposure therapy and virtual reality cognitive behavior therapy have become effective choices for patients with anxiety disorders and other phobias like fear of flying, claustrophobia, acrophobia or generalized social phobia” |
| Narrative review (mental health) | Maples-Keller JL, Bunnell BE, Kim SJ, et al. The use of virtual reality technology in the treatment of anxiety and other psychiatric disorders. <i>Harvard Review of Psychiatry</i> 2017; 25:103–113. ⁹ | Not reported | “VR has emerged as a viable tool to help in a number of different disorders, with the most strength of evidence for use in exposure therapy for patients with anxiety disorders, cue exposure therapy for patients with substance use disorders, and distraction for patients with acute pain requiring painful procedures.” |
| Systematic review (eating disorders) | de Carvalho M, Dias T, Duchesne M, et al. Virtual reality as a promising strategy in the assessment and treatment of bulimia nervosa and binge eating disorder: a systematic review. <i>Behavioral Sciences</i> 2017; 7:43. ¹⁷ | 19 studies | “Two different randomized, controlled trials have shown at one-year follow-up that VR had a higher efficacy than the gold standard in the field, i.e., cognitive behavioral therapy (CBT). In conclusion, based on the current available data VR-based environments may be considered a promising strategy for the assessment and treatment of BN and BED.” |
| Systematic review (clinical medicine) | Pourmand A, Davis S, Lee D, et al. Emerging utility of virtual reality as a multidisciplinary tool in clinical medicine. <i>Games for Health Journal</i> 2017; 6:263–270. ¹⁸ | 45 studies | “These articles provide data, which strongly support the hypothesis that VR simulations can enhance pain management (by reducing patient perception of pain and anxiety), can augment clinical training curricula and physical rehabilitation protocols (through immersive audiovisual environments), and can improve clinical assessment of cognitive function (through improved ecological validity).” |

(continued)

TABLE 1. (CONTINUED)

| <i>Review type</i> | <i>Article</i> | <i>Included studies</i> | <i>Conclusions (from the articles)</i> |
|--------------------------------------|---|-------------------------|---|
| Systematic review (autism) | Duffield TC, Parsons TD, Landry A, et al. Virtual environments as an assessment modality with pediatric ASD populations: a brief report. <i>Child Neuropsychology</i> 2017 Sep 13 [Epub ahead of print]. ²⁰ | 5 studies | “Psychometric comparisons of these tools for the neuropsychological assessment of pediatric individuals with ASD are lacking as the current review demonstrated, although the use of VEs. This is a particularly important area of future research considering most identification, and thus testing, treatment, and training occur in childhood for ASD.” |
| Narrative review (pediatrics) | Parsons TD, Riva G, Parsons S, et al. Virtual reality in pediatric psychology. <i>Pediatrics</i> 2017; 140:S86–S91. ²¹ | Not reported | “VR can offer safe, repeatable, and diversifiable interventions that can benefit assessments and learning in both typically developing children and children with disabilities. Research has also pointed to VR’s capacity to reduce children’s experience of aversive stimuli and reduce anxiety levels.” |
| Systematic review (autism) | Mesa-Gresa P, Gil-Gomez H, Lozano-Quilis JA, Gil-Gomez JA. Effectiveness of virtual reality for children and adolescents with autism spectrum disorder: an evidence-based systematic review. <i>Sensors (Basel)</i> 2018; 18:pii:E2486. | 31 studies | There is moderate evidence that VR-based treatments can help children with ASD. The lack of definitive findings does not allow us to state that VR-based treatments can improve the results of traditional treatments. Nevertheless, the promising results and the advantages of VR (especially considering ASD symptomatology) should encourage the scientific community to develop new VR-based treatments. |
| Systematic review (eating disorders) | Clus D, Larsen ME, Lemey C, Berrouguet S. The use of virtual reality in patients with eating disorders: systematic review. <i>J Med Internet Res</i> 2018; 20:e157. | 26 studies | Overall, VR techniques enable the evaluation of pathological eating behaviors and body image distortions. In addition to CBT, use of VR techniques by patients with eating disorders decreased their negative emotional responses to virtual food stimuli or exposure to their body shape. |

Three final articles explored the use of VR in the assessment and treatment of psychosis⁷ and in pain management.^{6,25} For psychosis, the available studies confirm the efficacy of VR for the multimodal assessment of cognitive functioning,⁷ including social cognition/competence⁶⁶ and hallucinations/paranoid ideations.⁶⁷ For treatment, even if the available studies are very promising,^{68–70} there is a lack of randomized controlled trials demonstrating whether VR is more efficacious or efficient than other interventions.⁷

In relation to the use of VR for pain management, older systematic reviews^{71,72} demonstrated the efficacy of VR distraction^{73–75} for reducing experimental pain,⁷⁶ as well as the one generated by burn injury care,^{77–79} chronic pain,^{80–82} and procedural pain.^{83–85} Hence, the first new one⁶ focused its analysis on the integrated use of VR with brain stimulation (transcranial direct-current stimulation) in pain management. Again, even if the level of clinical evidence is still low, a study⁸⁶ demonstrated the efficacy of this approach in reducing the severity of neuropathic pain and various neuropathic pain subtypes. Finally, the second new one,²⁵ suggests that VR may have a role in acutely painful procedures, even if further research is required.

Overall, this meta-review indicated that VR is a powerful clinical tool for behavioral health, able to provide effective assessment and treatment options for a variety of mental health disorders. Specifically, the 25 meta-analyses and systematic and narrative reviews indicated that VR compares favorably to existing treatments in anxiety disorders, eating and weight disorders, and pain management, with long-term effects that generalize to the real world. Moreover, they show the potential of VR as assessment tool with practical applications that range from social and cognitive deficits to addiction. Finally, they suggest a clinical potential in the treatment of psychosis and in the pediatric field, even if there is no definitive evidence for or against the use of VR.

The Effectiveness of VR as a Clinical Tool

An open issue not directly addressed by most of these articles is why VR is an effective clinical tool. In many articles, attention is focused on the high level of control and customization allowed by this technology.^{1,2,9,10,87} VR allows the level of fit between the content of the exposure and the feared stimuli to be optimized. Moreover, using it, the therapist has a total control—limited only by the specific features of the used software—on the contents of the experience. Finally, it offers a safer and more private context for the patient that facilitates his/her engagement.

Another important point suggested by different articles is the level of “presence” provided by the virtual experience. In fact, VR provides a digital place to the individual where he/she can be placed and live a synthetic but realistic experience.⁸⁸ As noted by some colleagues, VR can be considered an advanced imaginal system^{89,90}: an advanced form of imagery that is as effective as reality in inducing experiences and emotions. For example, as demonstrated by a recent meta-analysis, presence and anxiety are associated with each other during VRE therapy for the treatment of anxiety.⁹¹ This allows a level of self-reflectiveness that is both more predictable and controllable than the one offered by reality, but higher than the one provided by memory and imagination.¹ However, presence alone is necessary but not sufficient to

achieve benefit from VR therapy.⁹² As noted by Price and Anderson, “The results support presence as a conduit that enabled phobic anxiety to be expressed during exposure to a virtual environment. However, presence was not supported as contributing to treatment outcome. This suggests feeling present during exposure may be necessary but not sufficient to achieve benefit from VR exposure.”^{92(p750)}

A new argument that is introduced and discussed in this article is that VR shares with the brain the same basic mechanism: embodied simulations.^{43,93}

VR as Simulative Technology

An increasingly popular hypothesis—predictive coding^{94–96}—suggests that the brain actively maintains an internal model (simulation) of the body and the space around it, which provides predictions about the expected sensory input and tries to minimize the amount of prediction errors (or “surprise”). An in-depth discussion of these concepts is not offered here because authoritative and thorough accounts have been provided elsewhere.^{94–99} However, herein, the focus is on the concept of simulation introduced by this paradigm to understand better the links between the brain and VR.

One of the main tenets of predictive coding is that to regulate and control the body in the world effectively, the brain creates an embodied simulation of the body in the world. There are two main characteristics of this simulation. First, different from other internal models used in cognitive science—such as Tolman’s cognitive maps or Johhson-Laird’s internal models—they are simulations of sensory motor experiences. In this view, they include visceral/autonomic (interoceptive), motor (proprioceptive), and sensory (e.g., visual, auditory) information. Second, embodied simulations reactivate multimodal neural networks, which have produced the simulated/expected effect before.

This approach is used not only for actions, but also for concepts and emotions. Specifically, a concept is a group of distributed multimodal “patterns” of activity across different populations of neurons (motor, somatosensory, limbic, and frontal areas) that support a goal achievement.^{100,101} So, the simulation of a concept involves its reenactment in modality-specific brain areas. Moreover, the brain uses emotion concepts to categorize sensations. As underlined by Barrett, “That is, the brain constructs meaning by correctly anticipating (predicting and adjusting to) incoming sensations. Sensations are categorized so that they are (a) actionable in a situated way and therefore (b) meaningful, based on past experience. When past experiences of emotion (e.g., happiness) are used to categorize the predicted sensory array and guide action, then one experiences or perceives that emotion (happiness).”^{100(p9)} In this view, the feeling of presence in a space can be considered as an evolutive tool used to track the difference between the predicted sensations and those that are incoming from the sensory world, both externally and internally.^{93,102,103}

VR works in a similar way: it uses computer technology to create a simulated world that individuals can manipulate and explore as if they were in it. In other words, the VR experience tries to predict the sensory consequences of your movements, showing to you the same scene you will see in the real world. Specifically, VR hardware tracks the motion of the user, while VR software adjusts the images on the

user's display to reflect the changes produced by the motion in the virtual world. To achieve it, like the brain, the VR system maintains a model (simulation) of the body and the space around it. This prediction is then used to provide the expected sensory input using the VR hardware. Obviously, to be realistic, the VR model tries to mimic the brain model as much as possible: the more the VR model is similar to the brain model, the more the individual feels present in the VR world.^{93,104}

VR as Embodied Technology

As has just been seen, the brain creates multiple multisensory simulations to predict¹⁰⁰: (a) upcoming sensory events both inside and outside the body, and (b) the best action to deal with the impending sensory events. Moseley et al. suggested that these simulations are integrated with sensory data in the "body matrix," a coarse supramodal multisensory representation of the body and the space around it.^{105–107} Specifically, the contents of the body matrix are defined by top-down predictive signals, integrating the multisensory (motor and visceromotor) simulations of the causes of perceived sensory events.¹⁰⁸ The different simulations are then ranked and included in the body matrix according to their relevance for the intentions of the self (selective attention). At the same time, the content and the priority of the different simulations are corrected by bottom-up prediction errors that signal mismatches between predicted and actual contents of sensory events.¹⁰⁹

At the end of this process, the body matrix defines where the self is present, that is, in the body that our brain considers as the most likely to be its one.^{110–112} As underlined by Apps and Tsakiris, "The mental representation of the physical properties of one's self are, therefore, also probabilistic. That is, one's own body is the one that has the highest probability of being 'me,' since other objects are probabilistically less likely to evoke the same sensory inputs. In short, the notion that there is a 'self' is the most parsimonious and accurate explanation for sensory inputs."^{110(p88)}

If presence in the body is the outcome of different embodied simulations, and VR is a simulation technology, this suggests the possibility of altering the experience of the body by designing targeted virtual environments.¹¹³ In this view, VR can be defined as an "embodied technology" for its possibility of modifying the embodiment experience of its users.^{114–116} As noted by Riva et al., "using VR, subjects can experience the synthetic environment as if it was 'their surrounding world' (*incarnation*: the physical body is within a virtual environment) or can experience their synthetic avatars as if they were 'their own body' (*embodiment*: the physical body is replaced by the virtual one)."^{114(p9)} In other words, VR is able to fool the predictive coding mechanisms used by the brain generating the feeling of presence in a virtual body and in the digital space around it.

Up to now, VR has been used to simulate external reality, that is, to make people feel "real" what is actually not really there (i.e., the environment). However, the ability of VR to fool the predictive coding mechanisms that regulate the experience of the body also allows it to make people feel "real" what they are not. In other words, VR can offer new ways for structuring, augmenting, and/or replacing the experience of the body for clinical goals.^{114–116} Moreover, it may offer new embodied ways for assessing the functioning

of the brain^{117,118} by directly targeting the processes behind real-world behaviors.^{119–121}

But what is the real clinical potential of VR as an embodied technology? According to neuroscience, the body matrix^{105,106,122,123} serves to maintain the integrity of the body at both the homeostatic and psychological levels by supervising the cognitive and physiological resources necessary to protect the body and the space around it. Specifically, the body matrix plays a critical role in high-end cognitive processes such as motivation, emotion, social cognition, and self-awareness,^{124–126} while exerting a top-down modulation over basic physiological mechanisms such as thermoregulatory control^{127,128} and the immune system.¹²³

In this view, different authors^{114,116,129,130} have recently suggested that an altered functioning of the body matrix and/or its related processes might be the cause of different neurological and psychiatric conditions. If this is true, VR can be the core of a new trans-disciplinary research field—embodied medicine^{115,116}—the main goal of which is the use of advanced technology for altering the body matrix, with the goal of improving people's health and well-being.

As has been seen in the first section of this article, two different VR embodiment techniques—body swapping^{51,52} and reference frame shifting^{49,50}—are currently used in the treatment of eating and weight disorders. The first one, body swapping, replaces the contents of the bodily self-consciousness with synthetic ones (synthetic embodiment). This has been used in eating and weight disorders to improve the experience of the body in both clinical (anorexia and morbid obesity)^{131,132} and non-clinical subjects.^{133–135} Nevertheless, the potential of this approach is wider.¹³⁶ For example, it may offer a non-pharmacological way to reduce chronic pain. As has been seen in the first section of this article, VR distraction is effectively used to reduce acute pain. Nevertheless, according to Tsay et al., "available findings present compelling evidence for a novel multisensory and multimodal approach to therapies for chronic pain disorders"^{137(p249)} In this view, the use of VR embodiment may offer new treatment options for pain management.^{138–140}

Some studies have suggested the possibility of using VR body swapping to improve body perception disturbance in patients with complex regional pain syndrome.^{141,142}

The second technique, reference frame shifting, structures the individual's bodily self-consciousness through the focus and reorganization of its contents (mindful embodiment).^{50,143} It has been successfully used in different randomized trials in patients with eating and weight disorders^{54,55} to update the contents of their body memory. But again, its applications are probably wider. For example, Osimo et al. integrated body swapping (in the avatar of Sigmund Freud) and reference frame shifting to improve mood and happiness in a non-clinical sample.¹⁴³

A final emerging approach is the use of VR to augment the bodily experience through the awareness of internal (and difficult to sense) bodily information, or the mapping of a sensory channel to a different one—for example vision to touch or to hearing (augmented embodiment).^{144,145} For example, Suzuki et al.¹⁴⁶ implemented an innovative "cardiac rubber hand illusion" that combined computer-generated augmented reality with feedback of interoceptive information. Their results showed that the virtual-hand ownership is enhanced by cardio-visual feedback in time with the actual

heartbeat, supporting the use of this technique to improve emotion regulation.

VR as Cognitive Technology

VR is an embodied technology for its ability to modify the experience of the body. However, the body is not simply an object like any other; it has a special status.^{93,147,148} It is perceived in a multisensory way, from the outside (exteroception, the body perceived through the senses) as well as from within (inner body, including interoception, the sense of the physiological condition of the body; proprioception, the sense of the position of the body/body segments; and vestibular input, the sense of motion of the body) and from memory. This is true also for the simulative code used by the brain for creating concepts. As has been seen before, it integrates visceral/autonomic (interoceptive), motor (proprioceptive), and sensory information. If concepts are embodied simulations, and VR is an embodied technology, it should be possible to facilitate cognitive modeling and change by designing targeted virtual environments able to modify concepts both from outside and from inside.¹¹⁴

Nevertheless, there is a critical shortcoming that at the moment is limiting this possibility: VR simulates the external world/body but not the internal one. In fact, actual VR technology is very effective in reproducing the exteroceptive (external) features of the body using vision and hearing, but less effective in reproducing the other senses (i.e., touch and smell¹⁴⁹). It is partially effective in reproducing the proprioceptive (motor) features of the body using haptic technologies,¹⁵⁰ but it is not yet able to reproduce the interoceptive/ vestibular (internal) features of the body.

Recently, Riva et al.¹¹⁶ introduced the concept of “sonoception,” a novel noninvasive technological paradigm based on wearable acoustic and vibrotactile transducers, as a possible approach to structure, augment, and/or replace the contents of the inner body. This approach should be able to modulate the inner body (interoception, proprioception, and vestibular input) through the stimulation of both mechanoreceptors in different parts of the body—the stomach, the heart, the muscles—and the otolith organs of the vestibular system (see Fig. 2).

The first outcome of an integrated VR platform able to simulate both the external and the inner world is the possibility of structuring, augmenting, and/or replacing all the different experiential aspects of bodily self-consciousness, with clinical applications in the treatment of psychiatric disorders, such as depression^{151,152} or schizophrenia,^{153–155} and neurological disorders, such as chronic pain^{137,156} and neglect.^{157,158}

The final long-term outcome of this possibility may be the embodied virtual training machine described by the science-fiction thriller *The Matrix*. In this movie, the heroes, Trinity and Neo, learned how to fight martial-arts battles and drive motorcycles and helicopters by experiencing the bodily processes and concepts related to the skill through an embodied simulation.

Conclusions

The first article discussing a VR application in the field of behavioral health was published in 1995.¹⁵⁹ Now, more than 20 years later, VR is a reality in this field. This is the result of a meta-review presented in this article assessing the meta-analyses and systematic and narrative reviews published in this field in the last 22 months. Twenty-five different articles have demonstrated the clinical potential of this technology in both the diagnosis and the treatment of mental health disorders. Specifically, they indicate that VR compares favorably to existing treatments in anxiety disorders, eating and weight disorders, and pain management, with long-term effects that generalize to the real world.

But why is VR so effective? Here, the following answer is suggested: VR shares with the brain the same basic mechanism—embodied simulations.

According to neuroscience, to regulate and control the body in the world effectively, the brain creates an embodied simulation of the body in the world used to represent and predict actions, concepts, and emotions. Specifically, it is used to predict: (a) upcoming sensory events both inside and outside the body, and (b) the best action to deal with the impending sensory events.¹⁰⁰ There are two main characteristics of this simulation. First, it simulates sensory motor experiences, including visceral/autonomic (interoceptive),



FIG. 2. The technology of “sonoception.”

motor (proprioceptive), and sensory (e.g., visual, auditory) information. Second, embodied simulations reactivate multimodal neural networks which have produced the simulated/expected effect before.

VR works in a similar way: the VR experience tries to predict the sensory consequences of the individual's movements, providing to him/her the same scene he/she will see in the real world. To achieve this, the VR system, like the brain, maintains a model (simulation) of the body and the space around it.

If presence in the body is the outcome of different embodied simulations, and VR is a simulation technology, this suggests the possibility of altering the experience of the body by designing targeted virtual environments.¹¹³ In this view, VR can be defined as an “embodied technology” for its possibility of modifying the embodiment experience of its users.^{114–116} In other words, VR is able to fool the predictive coding mechanisms used by the brain, generating the feeling of presence in a virtual body and in the digital space around it.

Moreover, if concepts are embodied simulations, and VR is an embodied technology, it should be possible to facilitate cognitive modeling and change by designing targeted virtual environments able to modify concepts from both outside and inside.¹¹⁴

Nevertheless, at the moment, there is a critical shortcoming that is limiting this possibility: VR simulates the external world/body but not the internal one. Recently, Riva et al.¹¹⁶ introduced the concept of “sonoception” (www.sonoception.com), a novel noninvasive technological paradigm based on wearable acoustic and vibrotactile transducers able to stimulate both mechanoreceptors in different parts of the body—the stomach, the heart, the muscles—and the otolith organs of the vestibular system (see Fig. 2). The first outcome of this approach is the development of an interoceptive stimulator that is both able to assess interoceptive time perception in clinical patients¹⁶⁰ and to enhance heart rate variability (the short-term vagally mediated component—rMSSD) through the modulation of the subjects' parasympathetic system.¹⁶¹ The integration of these technologies with VR in a multi-sensory simulative platform will allow the modulation of both the external and internal bodily information, to structure, augment and/or replace the contents of our bodily self-consciousness.

In conclusion, even if VR is already a reality in behavioral health, the possibility of using it to simulate both the external and internal world may open new clinical options in the near future able to target the experience of the body and its related processes directly. Psychosomatics is an interdisciplinary field that explores the relationships between psychosocial, behavioral factors, and bodily processes. The long-term goal of the vision presented in this article is the use of simulative technologies—both simulating the external world and the internal one—to reverse engineer the psychosomatic processes that connect mind and body. If achieved, this perspective will provide a radically new meaning to the classical Juvenal's Latin dictum “*Mens sana in corpore sano*” (a healthy mind in a healthy body) by allowing a new trans-disciplinary research field—“Embodied Medicine”^{115,116}—that will use advanced multi-sensory technologies to alter bodily processes for enhancing homeostasis and well-being.

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References

1. Riva G, Baños RM, Botella C, et al. Transforming experience: the potential of augmented reality and virtual reality for enhancing personal and clinical change. *Frontiers in Psychiatry* 2016; 7:164.
2. Freeman D, Reeve S, Robinson A, et al. Virtual reality in the assessment, understanding, and treatment of mental health disorders. *Psychological Medicine* 2017; 47:2393–2400.
3. Riva G. Letter to the editor: virtual reality in the treatment of eating and weight disorders. *Psychological Medicine* 2017; 47:2567–2568.
4. van Bennekom MJ, de Koning PP, Denys D. Virtual reality objectifies the diagnosis of psychiatric disorders: a literature review. *Frontiers in Psychiatry* 2017; 8:163.
5. Lindner P, Miloff A, Hamilton W, et al. Creating state of the art, next-generation virtual reality exposure therapies for anxiety disorders using consumer hardware platforms: design considerations and future directions. *Cognitive Behaviour Therapy* 2017; 46:404–420.
6. Massetti T, Crocetta TB, Silva TDD, et al. Application and outcomes of therapy combining transcranial direct current stimulation and virtual reality: a systematic review. *Disability & Rehabilitation: Assistive Technology* 2017; 12:551–559.
7. Rus-Calafell M, Garety P, Sason E, et al. Virtual reality in the assessment and treatment of psychosis: a systematic review of its utility, acceptability and effectiveness. *Psychological Medicine* 2017; 48:362–391.
8. Botella C, Fernández-Álvarez J, Guillén V, et al. Recent progress in virtual reality exposure therapy for phobias: a systematic review. *Current Psychiatry Reports* 2017; 19:42.
9. Maples-Keller JL, Bunnell BE, Kim SJ, et al. The use of virtual reality technology in the treatment of anxiety and other psychiatric disorders. *Harvard Review of Psychiatry* 2017; 25:103–113.
10. Maples-Keller JL, Yasinski C, Manjin N, et al. Virtual reality-enhanced extinction of phobias and post-traumatic stress. *Neurotherapeutics* 2017; 14:554–563.
11. Cardoso RAI, David OA, David DO. Virtual reality exposure therapy in flight anxiety: a quantitative meta-analysis. *Computers in Human Behavior* 2017; 72:371–380.
12. Castelnuovo G, Pietrabissa G, Manzoni GM, et al. Cognitive behavioral therapy to aid weight loss in obese patients: current perspectives. *Psychology Research & Behavior Management* 2017; 10:165–173.
13. Paul L, Van Der Heiden C, Hoek HW. Cognitive behavioral therapy and predictors of weight loss in bariatric surgery patients. *Current Opinion in Psychiatry* 2017; 30:474–479.

14. Dascal J, Reid M, Ishak WW, et al. Virtual reality and medical inpatients: a systematic review of randomized, controlled trials. *Innovations in Clinical Neuroscience* 2017; 14:14–21.
15. Li L, Yu F, Shi D, et al. Application of virtual reality technology in clinical medicine. *American Journal of Translational Research* 2017; 9:3867–3880.
16. Arroll B, Wallace HB, Mount V, et al. A systematic review and meta-analysis of treatments for acrophobia. *The Medical Journal of Australia* 2017; 206:263–267.
17. de Carvalho M, Dias T, Duchesne M, et al. Virtual reality as a promising strategy in the assessment and treatment of bulimia nervosa and binge eating disorder: a systematic review. *Behavioral Sciences* 2017; 7:43.
18. Pourmand A, Davis S, Lee D, et al. Emerging utility of virtual reality as a multidisciplinary tool in clinical medicine. *Games for Health Journal* 2017; 6:263–270.
19. Mishkind MC, Norr AM, Katz AC, et al. Review of virtual reality treatment in psychiatry: evidence versus current diffusion and use. *Current Psychiatry Reports* 2017; 19:80.
20. Duffield TC, Parsons TD, Landry A, et al. Virtual environments as an assessment modality with pediatric ASD populations: a brief report. *Child Neuropsychology* 2017 Sep 13 [Epub ahead of print]; DOI: 10.1080/09297049.2017.1375473.
21. Parsons TD, Riva G, Parsons S, et al. Virtual reality in pediatric psychology. *Pediatrics* 2017; 140:S86–S91.
22. Jerdan SW, Grindle M, van Woerden HC, Kamel Boulos MN. Head-mounted virtual reality and mental health: critical review of current research. *JMIR Serious Games* 2018; 6:e14.
23. Clus D, Larsen ME, Lemey C, Berrouiguet S. The use of virtual reality in patients with eating disorders: systematic review. *Journal of Medical Internet Research* 2018; 20:e157.
24. Mesa-Gresa P, Gil-Gomez H, Lozano-Quilis JA, Gil-Gomez JA. Effectiveness of virtual reality for children and adolescents with autism spectrum disorder: an evidence-based systematic review. *Sensors* 2018; 18:pii:E2486.
25. Chan E, Foster S, Sambell R, Leong P. Clinical efficacy of virtual reality for acute procedural pain management: a systematic review and meta-analysis. *PLoS One* 2018; 13:e0200987.
26. Rothbaum BO, Rizzo AS, Difede J. Virtual reality exposure therapy for combat-related posttraumatic stress disorder. *Annals of the New York Academy of Sciences* 2010; 1208:126–132.
27. Wiederhold BK, Wiederhold MD. Three-year follow-up for virtual reality exposure for fear of flying. *CyberPsychology & Behavior* 2003; 6:441–445.
28. McLay RN, Wood DP, Webb-Murphy JA, et al. A randomized, controlled trial of virtual reality-graded exposure therapy for post-traumatic stress disorder in active duty service members with combat-related post-traumatic stress disorder. *Cyberpsychology, Behavior, & Social Networking* 2011; 14:223–239.
29. Repetto C, Gorini A, Vigna C, et al. The use of biofeedback in clinical virtual reality: the INTREPID project. *Journal of Visualized Experiments* 2009 Nov 12 [Epub ahead of print]; DOI: 10.3791/1554.
30. Wiederhold BK, Wiederhold MD. Clinical observations during virtual reality therapy for specific phobias. *CyberPsychology & Behavior* 1999; 2:161–168.
31. Rothbaum BO, Hodges L, Smith S, et al. A controlled study of virtual reality exposure therapy for the fear of flying. *Journal of Consulting & Clinical Psychology* 2000; 68:1020–1026.
32. Parsons TD, Rizzo AA. Affective outcomes of virtual reality exposure therapy for anxiety and specific phobias: a meta-analysis. *Journal of Behavior Therapy & Experimental Psychiatry* 2008; 39:250–261.
33. Goncalves R, Pedrozo AL, Coutinho ES, et al. Efficacy of virtual reality exposure therapy in the treatment of PTSD: a systematic review. *PLoS One* 2012; 7:e48469.
34. Botella C, García-Palacios A, Villa H, et al. Virtual reality exposure in the treatment of panic disorder and agoraphobia: a controlled study. *Clinical Psychology & Psychotherapy* 2007; 14:164–175.
35. Anderson PL, Price M, Edwards SM, et al. Virtual reality exposure therapy for social anxiety disorder: a randomized controlled trial. *Journal of Consulting & Clinical Psychology* 2013; 81:751–760.
36. Gaggioli A, Pallavicini F, Morganti L, et al. Experiential virtual scenarios with real-time monitoring (interreality) for the management of psychological stress: a block randomized controlled trial. *Journal of Medical Internet Research* 2014; 16:e167.
37. Repetto C, Gaggioli A, Pallavicini F, et al. Virtual reality and mobile phones in the treatment of generalized anxiety disorders: a Phase-2 clinical trial. *Personal & Ubiquitous Computing* 2013; 17:253–260.
38. Wiederhold BK, Riva G, Gutierrez-Maldonado J. Virtual reality in the assessment and treatment of weight-related disorders. *Cyberpsychology, Behavior, & Social Networking* 2016; 19:67–73.
39. Pla-Sanjuanelo J, Ferrer-García M, Vilalta-Abella F, et al. Testing virtual reality-based cue-exposure software: which cue-elicited responses best discriminate between patients with eating disorders and healthy controls? *Eating and Weight Disorders* 2017 Jul 27 [Epub ahead of print]; DOI: 10.1007/s40519-017-0419-4.
40. Ferrer-Garcia M, Gutierrez-Maldonado J, Pla-Sanjuanelo J, et al. A randomised controlled comparison of second-level treatment approaches for treatment-resistant adults with bulimia nervosa and binge eating disorder: assessing the benefits of virtual reality cue exposure therapy. *European Eating Disorders Review* 2017; 25:479–490.
41. Riva G. Modifications of body image induced by virtual reality. *Perceptual & Motor Skills* 1998; 86:163–170.
42. Riva G, Bacchetta M, Baruffi M, et al. Virtual reality-based experiential cognitive treatment of obesity and binge-eating disorders. *Clinical Psychology & Psychotherapy* 2000; 7: 209–219.
43. Riva G, Gaudio S. Locked to a wrong body: eating disorders as the outcome of a primary disturbance in multisensory body integration. *Consciousness & Cognition* 2018; 59:57–59.
44. Riva G, Gaudio S, Dakanalis A. The neuropsychology of self objectification. *European Psychologist* 2015; 20:34–43.
45. Riva G. Out of my real body: cognitive neuroscience meets eating disorders. *Frontiers in Human Neuroscience* 2014; 8:236.
46. Riva G. Neuroscience and eating disorders: the allocentric lock hypothesis. *Medical Hypotheses* 2012; 78:254–257.
47. Serino S, Dakanalis A, Gaudio S, et al. Out of body, out of space: impaired reference frame processing in eating disorders. *Psychiatry Research* 2015; 230:732–734.
48. Riva G, Dakanalis A. Altered processing and integration of multisensory bodily representations and signals in

- eating disorders: a possible path toward the understanding of their underlying causes. *Frontiers in Human Neuroscience* 2018; 12:49.
49. Akhtar S, Justice LV, Loveday C, et al. Switching memory perspective. *Consciousness & Cognition* 2017; 56:50–57.
 50. Riva G. The key to unlocking the virtual body: virtual reality in the treatment of obesity and eating disorders. *Journal of Diabetes Science & Technology* 2011; 5:283–292.
 51. Normand JM, Giannopoulos E, Spanlang B, et al. Multi-sensory stimulation can induce an illusion of larger belly size in immersive virtual reality. *Plos One* 2011; 6:e16128.
 52. Gutiérrez-Maldonado J, Wiederhold BK, Riva G. Future directions: how virtual reality can further improve the assessment and treatment of eating disorders and obesity. *Cyberpsychology, Behavior, & Social Networking* 2016; 19:148–153.
 53. Marco JH, Perpina C, Botella C. Effectiveness of cognitive behavioral therapy supported by virtual reality in the treatment of body image in eating disorders: one year follow-up. *Psychiatry Research* 2013; 209:619–625.
 54. Manzoni GM, Cesa GL, Bacchetta M, et al. Virtual reality-enhanced cognitive-behavioral therapy for morbid obesity: a randomized controlled study with 1 year follow-up. *Cyberpsychology, Behavior, & Social Networking* 2016; 19:134–140.
 55. Cesa GL, Manzoni GM, Bacchetta M, et al. Virtual reality for enhancing the cognitive behavioral treatment of obesity with binge eating disorder: randomized controlled study with one-year follow-up. *Journal of Medical Internet Research* 2013; 15:e113.
 56. Marta F-G, Joana P-S, Antonios D, et al. A randomized trial of virtual reality-based cue exposure second-level therapy and cognitive behavior second-level therapy for bulimia nervosa and binge-eating disorder: outcome at six-month followup. *Cyberpsychology, Behavior, & Social Networking* 2018 July 30 [Epub ahead of print]; DOI: 10.1089/cyber.2017.0675.
 57. Parsons S. Authenticity in virtual reality for assessment and intervention in autism: a conceptual review. *Educational Research Review* 2016; 19:138–157.
 58. Negut A, Jurma AM, David D. Virtual-reality-based attention assessment of ADHD: ClinicaVR: classroom-CPT versus a traditional continuous performance test. *Child Neuropsychology* 2017; 23:692–712.
 59. Pollak Y, Weiss PL, Rizzo AA, et al. The utility of a continuous performance test embedded in virtual reality in measuring ADHD-related deficits. *Journal of Developmental & Behavioral Pediatrics* 2009; 30:2–6.
 60. Hone-Blanchet A, Wensing T, Fecteau S. The use of virtual reality in craving assessment and cue-exposure therapy in substance use disorders. *Frontiers in Human Neuroscience* 2014; 8:844.
 61. Bordnick PS, Graap KM, Copp HL, et al. Virtual reality cue reactivity assessment in cigarette smokers. *CyberPsychology & Behavior* 2005; 8:487–492.
 62. Lee J, Lim Y, Graham SJ, et al. Nicotine craving and cue exposure therapy by using virtual environments. *CyberPsychology & Behavior* 2004; 7:705–713.
 63. Bordnick PS, Traylor A, Copp HL, et al. Assessing reactivity to virtual reality alcohol based cues. *Addictive Behaviors* 2008; 33:743–756.
 64. Ledoux T, Nguyen AS, Bakos-Block C, et al. Using virtual reality to study food cravings. *Appetite* 2013; 71:396–402.
 65. Saladin ME, Brady KT, Graap K, et al. A preliminary report on the use of virtual reality technology to elicit craving and cue reactivity in cocaine dependent individuals. *Addictive Behaviors* 2006; 31:1881–1894.
 66. Gutiérrez-Maldonado J, Rus-Calafell M, Marquez-Rejón S, et al. Associations between facial emotion recognition, cognition and alexithymia in patients with schizophrenia: comparison of photographic and virtual reality presentations. *Studies in Health Technology & Informatics* 2012; 181:88–92.
 67. Stinson K, Valmaggia LR, Antley A, et al. Cognitive triggers of auditory hallucinations: an experimental investigation. *Journal of Behavioral Therapy & Experimental Psychiatry* 2010; 41:179–184.
 68. Freeman D, Bradley J, Antley A, et al. Virtual reality in the treatment of persecutory delusions: randomised controlled experimental study testing how to reduce delusional conviction. *British Journal of Psychiatry* 2016; 209:62–67.
 69. Gega L, White R, Clarke T, et al. Virtual environments using video capture for social phobia with psychosis. *Cyberpsychology, Behavior, & Social Networking* 2013; 16:473–479.
 70. Leff J, Williams G, Huckvale MA, et al. Computer-assisted therapy for medication-resistant auditory hallucinations: proof-of-concept study. *British Journal of Psychiatry* 2013; 202:428–433.
 71. Malloy KM, Milling LS. The effectiveness of virtual reality distraction for pain reduction: a systematic review. *Clinical Psychology Review* 2010; 30:1011–1018.
 72. Morris LD, Louw QA, Grimmer-Somers K. The effectiveness of virtual reality on reducing pain and anxiety in burn injury patients: a systematic review. *The Clinical Journal of Pain* 2009; 25:815–826.
 73. Wiederhold BK, Soomro A, Riva G, et al. Future directions: advances and implications of virtual environments designed for pain management. *Cyberpsychology, Behavior, & Social Networking* 2014; 17:414–422.
 74. Sulea C, Soomro A, Boyd C, et al. Pain management in virtual reality: a comprehensive research chart. *Cyberpsychology, Behavior, & Social Networking* 2014; 17:402–413.
 75. Li A, Montano Z, Chen VJ, et al. Virtual reality and pain management: current trends and future directions. *Pain Management* 2011; 1:147–157.
 76. Keefe FJ, Huling DA, Coggins MJ, et al. Virtual reality for persistent pain: a new direction for behavioral pain management. *Pain* 2012; 153:2163–2166.
 77. Schmitt YS, Hoffman HG, Blough DK, et al. A randomized, controlled trial of immersive virtual reality analgesia, during physical therapy for pediatric burns. *Burns* 2011; 37:61–68.
 78. Hoffman HG, Richards TL, Coda B, et al. Modulation of thermal pain-related brain activity with virtual reality: evidence from fMRI. *Neuroreport* 2004; 15:1245–1248.
 79. Hoffman HG, Richards TL, Van Oostrom T, et al. The analgesic effects of opioids and immersive virtual reality distraction: evidence from subjective and functional brain imaging assessments. *Anesthesia & Analgesia* 2007; 105:1776–1783, table of contents.
 80. Wiederhold BK, Gao K, Sulea C, et al. Virtual reality as a distraction technique in chronic pain patients. *Cyberpsychology, Behavior, & Social Networking* 2014; 17:346–352.
 81. Parsons TD, Trost Z. (2014) Virtual reality graded exposure therapy as treatment for pain-related fear and

- disability in chronic pain. In Ma M, Jain L, Anderson P, eds. *Virtual, augmented reality and serious games for healthcare 1*. Intelligent Systems Reference Library, vol. 68. Berlin: Springer, pp. 523–546.
82. Jin W, Choo A, Gromala D, et al. A virtual reality game for chronic pain management: a randomized, controlled clinical study. *Studies in Health Technology & Informatics* 2016; 220:154–160.
 83. Hua Y, Qiu R, Yao WY, et al. The effect of virtual reality distraction on pain relief during dressing changes in children with chronic wounds on lower limbs. *Pain Management Nursing* 2015; 16:685–691.
 84. Wiederhold MD, Gao K, Wiederhold BK. Clinical use of virtual reality distraction system to reduce anxiety and pain in dental procedures. *Cyberpsychology, Behavior, & Social Networking* 2014; 17:359–365.
 85. Mosso-Vazquez JL, Gao K, Wiederhold BK, et al. Virtual reality for pain management in cardiac surgery. *Cyberpsychology, Behavior, & Social Networking* 2014; 17:371–378.
 86. Soler MD, Kumru H, Pelayo R, et al. Effectiveness of transcranial direct current stimulation and visual illusion on neuropathic pain in spinal cord injury. *Brain* 2010; 133: 2565–2577.
 87. Pallavicini F, Ferrari A, Zini A, et al. (2017) What distinguishes a traditional gaming experience from one in virtual reality? An exploratory study. In Ahram T, Falcão C, eds. *Advances in human factors in wearable technologies and game design*. Cham, Switzerland: Springer, pp. 225–231.
 88. Riva G, Botella C, Baños R, et al. (2015) Presence-inducing media for mental health applications. In Lombard M, Biocca F, Freeman J, et al., eds. *Immersed in media*. New York: Springer, pp. 283–332.
 89. Vincelli F, Riva G. Virtual reality as a new imaginative tool in psychotherapy. *Studies in Health Technology & Informatics* 2000; 70:356–358.
 90. Riva G, Molinari E, Vincelli F. Interaction and presence in the clinical relationship: virtual reality (VR) as communicative medium between patient and therapist. *IEEE Transactions on Information Technology in Biomedicine* 2002; 6:198–205.
 91. Ling Y, Nefs HT, Morina N, et al. A meta-analysis on the relationship between self-reported presence and anxiety in virtual reality exposure therapy for anxiety disorders. *PLoS One* 2014; 9:e96144.
 92. Price M, Anderson P. The role of presence in virtual reality exposure therapy. *Journal of Anxiety Disorders* 2007; 21:742–751.
 93. Riva G. The neuroscience of body memory: from the self through the space to the others. *Cortex* 2017 Jul 25 [Epub ahead of print]; DOI: 10.1016/j.cortex.2017.07.013.
 94. Friston K. The free-energy principle: a unified brain theory? *Nature Reviews Neuroscience* 2010; 11:127–138.
 95. Friston K. Embodied inference and spatial cognition. *Cognitive Processing* 2012; 13:S171–177.
 96. Clark A. Whatever next? Predictive brains, situated agents, and the future of cognitive science. *Behavioral & Brain Sciences* 2013; 36:181–204.
 97. Talsma D. Predictive coding and multisensory integration: an attentional account of the multisensory mind. *Frontiers in Integrative Neuroscience* 2015; 9:19.
 98. Hohwy J. (2013) *The predictive mind*. Oxford: Oxford University Press.
 99. Clark A. (2016) *Surfing uncertainty: prediction, action, and the embodied mind*. Oxford: Oxford University Press.
 100. Barrett LF. The theory of constructed emotion: an active inference account of interoception and categorization. *Social Cognitive & Affective Neuroscience* 2017; 12:1–23.
 101. Barsalou LW. Situated simulation in the human conceptual system. *Language & Cognitive Processes* 2003; 18: 513–562.
 102. Riva G, Waterworth JA, Waterworth EL, et al. From intention to action: the role of presence. *New Ideas in Psychology* 2011; 29:24–37.
 103. Riva G, Mantovani F. From the body to the tools and back: a general framework for presence in mediated interactions. *Interacting with Computers* 2012; 24:203–210.
 104. Sanchez-Vives MV, Slater M. From presence to consciousness through virtual reality. *Nature Reviews Neuroscience* 2005; 6:332–339.
 105. Moseley GL, Gallace A, Spence C. Bodily illusions in health and disease: physiological and clinical perspectives and the concept of a cortical “body matrix.” *Neuroscience & Biobehavioral Reviews* 2012; 36:34–46.
 106. Gallace A, Spence C. (2014) *In touch with the future: the sense of touch from cognitive neuroscience to virtual reality*. Oxford: Oxford University Press.
 107. Sedda A, Tonin D, Salvato G, et al. Left caloric vestibular stimulation as a tool to reveal implicit and explicit parameters of body representation. *Consciousness & Cognition* 2016; 41:1–9.
 108. Friston K, Daunizeau J, Kilner J, et al. Action and behavior: a free-energy formulation. *Biological Cybernetics* 2010; 102:227–260.
 109. Friston K. The free-energy principle: a rough guide to the brain? *Trends in Cognitive Sciences* 2009; 13:293–301.
 110. Apps MA, Tsakiris M. The free-energy self: a predictive coding account of self-recognition. *Neuroscience & Biobehavioral Reviews* 2014; 41:85–97.
 111. Holmes NP, Spence C. The body schema and the multisensory representation(s) of peripersonal space. *Cognitive Processing* 2004; 5:94–105.
 112. Serino S, Scarpina F, Dakanalis A, et al. The role of age on multisensory bodily experience: an experimental study with a virtual reality full-body illusion. *Cyberpsychology, Behavior, & Social Networking* 2018; 21:304–310.
 113. Oliveira ECD, Bertrand P, Lesur MER, et al. Virtual body swap: a new feasible tool to be explored in health and education. In *2016 XVIII Symposium on Virtual and Augmented Reality (SVR 2016)*. New York: Institute of Electrical and Electronics Engineers, pp. 81–89.
 114. Riva G. From virtual to real body: virtual reality as embodied technology. *Journal of Cybertherapy & Rehabilitation* 2008; 1:7–22.
 115. Riva G. (2016) Embodied medicine: what human computer confluence can offer to health care. In Gaggioli A, Ferscha A, Riva G, et al., eds. *Human computer confluence: transforming human experience through symbiotic technologies*. Warsaw, Poland: De Gruyter Open, pp. 55–79.
 116. Riva G, Serino S, Di Lernia D, et al. Embodied medicine: mens sana in corpore virtuale sano. *Frontiers in Human Neuroscience* 2017; 11:120.
 117. Parsons TD. Virtual reality for enhanced ecological validity and experimental control in the clinical, affective and social

- neurosciences. *Frontiers in Human Neuroscience* 2015; 9: 660.
118. Parsons T, Gaggioli A, Riva G. Virtual reality for research in social neuroscience. *Brain Sciences* 2017; 7:42.
 119. Serino S, Baglio F, Rossetto F, et al. Picture Interpretation Test (PIT) 360°: an innovative measure of executive functions. *Scientific Reports* 2017; 7:16000.
 120. Cipresso P. Modeling behavior dynamics using computational psychometrics within virtual worlds. *Frontiers in Psychology* 2015; 6:1725.
 121. Cipresso P, Serino S, Riva G. Psychometric assessment and behavioral experiments using a free virtual reality platform and computational science. *BMC Medical Informatics & Decision Making* 2016; 16:37.
 122. Finotti G, Migliorati D, Costantini M. Multisensory integration, bodily self-consciousness and disorders of the immune system. *Brain, Behavior, & Immunity* 2015; 49:e31.
 123. Finotti G, Costantini M. Multisensory body representation in autoimmune diseases. *Scientific Reports* 2016; 6:21074.
 124. Tsakiris M. The multisensory basis of the self: from body to identity to others. *Quarterly Journal of Experimental Psychology* 2017; 70:597–609.
 125. Maister L, Slater M, Sanchez-Vives MV, et al. Changing bodies changes minds: owning another body affects social cognition. *Trends in Cognitive Sciences* 2015; 19:6–12.
 126. Maister L, Sebanz N, Knoblich G, et al. Experiencing ownership over a dark-skinned body reduces implicit racial bias. *Cognition* 2013; 128:170–178.
 127. Macaudo G, Bertolini G, Palla A, et al. Binding body and self in visuo-vestibular conflicts. *European Journal of Neuroscience* 2015; 41:810–817.
 128. Gallace A, Soravia G, Cattaneo Z, et al. Temporary interference over the posterior parietal cortices disrupts thermoregulatory control in humans. *PLoS One* 2014; 9:e88209.
 129. Brugger P, Lenggenhager B. The bodily self and its disorders: neurological, psychological and social aspects. *Current Opinion in Neurology* 2014; 27:644–652.
 130. Tsakiris M, Critchley H. Interoception beyond homeostasis: affect, cognition and mental health. *Philosophical Transactions of the Royal Society B* 2016; 371.
 131. Keizer A, van Elburg A, Helms R, et al. A virtual reality full body illusion improves body image disturbance in anorexia nervosa. *PLoS One* 2016; 11:e0163921.
 132. Serino S, Scarpina F, Keizer A, et al. A novel technique for improving bodily experience in a non-operable super-super obesity case. *Frontiers in Psychology* 2016; 7:837.
 133. Serino S, Pedroli E, Keizer A, et al. Virtual reality body swapping: a tool for modifying the allocentric memory of the body. *Cyberpsychology, Behavior, & Social Networking* 2016; 19:127–133.
 134. Preston C, Ehrsson HH. Illusory changes in body size modulate body satisfaction in a way that is related to non-clinical eating disorder psychopathology. *Plos One* 2014; 9:e85773.
 135. Preston C, Ehrsson HH. Illusory obesity triggers body dissatisfaction responses in the insula and anterior cingulate cortex. *Cerebral Cortex* 2016; 26:4450–4460.
 136. Serino S, Dakanalis A. Bodily illusions and weight-related disorders: clinical insights from experimental research. *Annals of Physical & Rehabilitation Medicine* 2017; 60: 217–219.
 137. Tsay A, Allen TJ, Proske U, et al. Sensing the body in chronic pain: a review of psychophysical studies implicating altered body representation. *Neuroscience & Biobehavioral Reviews* 2015; 52:221–232.
 138. Romano D, Llobera J, Blanke O. Size and viewpoint of an embodied virtual body impact the processing of painful stimuli. *Journal of Pain* 2016; 17:350–358.
 139. Pazzaglia M, Haggard P, Scivoletto G, et al. Pain and somatic sensation are transiently normalized by illusory body ownership in a patient with spinal cord injury. *Restorative Neurology & Neuroscience* 2016; 34:603–613.
 140. Sarig Bahat H, Takasaki H, Chen XQ, et al. Cervical kinematic training with and without interactive VR training for chronic neck pain—a randomized clinical trial. *Manual Therapy* 2015; 20:68–78.
 141. Hwang H, Cho S, Lee JH. The effect of virtual body swapping with mental rehearsal on pain intensity and body perception disturbance in complex regional pain syndrome. *International Journal of Rehabilitation Research* 2014; 37: 167–172.
 142. Jeon B, Cho S, Lee JH. Application of virtual body swapping to patients with complex regional pain syndrome: a pilot study. *Cyberpsychology, Behavior, & Social Networking* 2014; 17:366–370.
 143. Osimo SA, Pizarro R, Spanlang B, et al. Conversations between self and self as Sigmund Freud—a virtual body ownership paradigm for self counselling. *Scientific Reports* 2015; 5.
 144. Waterworth JA, Waterworth EL. (2014) Altered, expanded and distributed embodiment: the three stages of interactive presence. In Riva G, Waterworth JA, Murray D, eds. *Interacting with presence: HCI and the sense of presence in computer-mediated environments*. Berlin: De Gruyter Open, pp. 36–50.
 145. Duquette P. Increasing our insular world view: interoception and psychopathology for psychotherapists. *Frontiers in Neuroscience* 2017; 11:135.
 146. Suzuki K, Garfinkel SN, Critchley HD, et al. Multisensory integration across exteroceptive and interoceptive domains modulates self-experience in the rubber-hand illusion. *Neuropsychologia* 2013; 51:2909–2917.
 147. Aspell JE, Lenggenhager B, Blanke O. (2012) Multisensory perception and bodily self-consciousness. From out-of-body to inside-body experience. In Murray MM, Wallace MT, eds. *The neural bases of multisensory processes*. Boca Raton, FL: CRC Press, ch. 24.
 148. Blanke O. Multisensory brain mechanisms of bodily self-consciousness. *Nature Reviews Neuroscience* 2012; 13: 556–571.
 149. Serrano B, Baños RM, Botella C. Virtual reality and stimulation of touch and smell for inducing relaxation: a randomized controlled trial. *Computers in Human Behavior* 2016; 55:1–8.
 150. Adams RJ, Hannaford B. Control law design for haptic interfaces to virtual reality. *IEEE Transactions on Control Systems Technology* 2002; 10:3–13.
 151. Barrett LF, Quigley KS, Hamilton P. An active inference theory of allostasis and interoception in depression. *Philosophical Transactions of the Royal Society B* 2016; 371.
 152. Wheatley J, Brewin CR, Patel T, et al. I'll believe it when I can see it: imagery rescripting of intrusive sensory memories in depression. *Journal of Behavior Therapy & Experimental Psychiatry* 2007; 38:371–385.
 153. Postmes L, Sno HN, Goedhart S, et al. Schizophrenia as a self-disorder due to perceptual incoherence. *Schizophrenia Research* 2014; 152:41–50.

154. Ferri F, Costantini M, Salone A, et al. Upcoming tactile events and body ownership in schizophrenia. *Schizophrenia Research* 2014; 152:51–57.
155. Klaver M, Dijkerman HC. Bodily experience in schizophrenia: factors underlying a disturbed sense of body ownership. *Frontiers in Human Neuroscience* 2016; 10:305.
156. Di Lernia D, Serino S, Riva G. Pain in the body. Altered interoception in chronic pain conditions: A systematic review. *Neuroscience & Biobehavioral Reviews* 2016; 71: 328–341.
157. Bolognini N, Convento S, Casati C, et al. Multisensory integration in hemianopia and unilateral spatial neglect: evidence from the sound induced flash illusion. *Neuropsychologia* 2016; 87:134–143.
158. Lenggenhager B, Loetscher T, Kavan N, et al. Paradoxical extension into the contralesional hemispace in spatial neglect. *Cortex* 2012; 48:1320–1328.
159. Rothbaum BO, Hodges LF, Kooper R, et al. Effectiveness of computer-generated (virtual reality) graded exposure in the treatment of acrophobia. *American Journal of Psychiatry* 1995; 152:626–628.
160. Di Lernia D, Serino S, Pezzulo G, et al. Feel the time. Time perception as a function of interoceptive processing. *Frontiers in Human Neuroscience* 2018; 12:74.
161. Di Lernia D, Cipresso P, Pedroli E, Riva G. Toward an embodied medicine: a portable device with programmable interoceptive stimulation for heart rate variability enhancement. *Sensors* 2018; 18:pii:E2469.
162. Uman LS. Systematic reviews and meta-analyses. *Journal of the Canadian Academy of Child & Adolescent Psychiatry* 2011; 20:57–59.

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