Virtual reality in neuroscience research and therapy

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Abstract | Virtual reality (VR) environments are increasingly being used by neuroscientists to simulate natural events and social interactions. VR creates interactive, multimodal sensory stimuli that offer unique advantages over other approaches to neuroscientific research and applications. VR's compatibility with imaging technologies such as functional MRI allows researchers to present multimodal stimuli with a high degree of ecological validity and control while recording changes in brain activity. Therapists, too, stand to gain from progress in VR technology, which provides a high degree of control over the therapeutic experience. Here we review the latest advances in VR technology and its applications in neuroscience research.

Ecological validity
Refers to experimental conditions that are reasonably similar to those in a real-world setting. In virtual environments, contextually rich simulations with multiple sensory cues might be considered to have greater ecological validity than environments that are limited to only the necessary and sufficient features for an experiment.

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An enduring tension exists between ecological validity and experimental control in psychology and neuroscience research. Experimentalists have long used text-, graphic- or computer-based abstractions of real-world objects or situations when submitting experimental variables to study. Such highly controlled but contextually impoverished stimuli greatly simplify the world for research but leave us guessing as to their generalizability. Conversely, therapists and practising psychologists often relinquish control in order to observe or influence behaviour in complex real-world surroundings.

Virtual reality (VR) provides a middle ground, supporting naturalistic and contextually rich scenarios along with an exacting degree of control over key variables. VR has value for studying processes such as neuronal connectivity, developmental dynamics, neuromuscular output and perhaps even the initiation of molecular cascades, and as reviewed below, VR continues to garner validation as a therapeutic application. There have been several reviews on the uses of VR for neuroscience-related work[1–8]. Here, we focus on the most recent applications of VR, highlighting those that combine VR with brain imaging, as well as developments in VR systems for animal research.

State of the art

VR system components work in concert to create sensory illusions that produce a more or less believable simulation of reality[9]. The goal is to foster brain and behavioural responses in the virtual world that are analogous to those that occur in the real world.

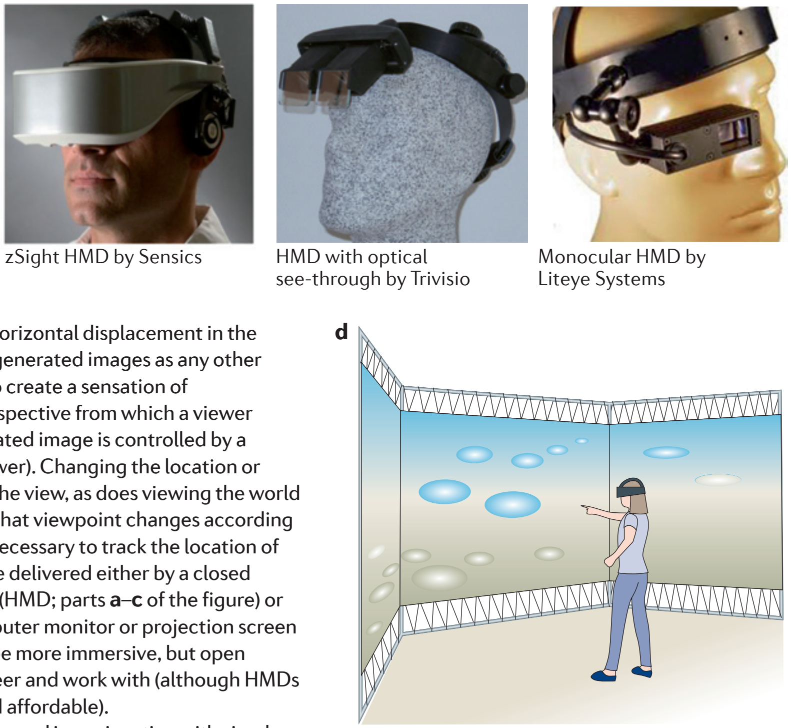
Sensory stimulation comes in many forms (BOX 1). VR systems are best at displaying visual and auditory information. Increasingly, these are approaching the sensory vividness of the physical environment. In addition, VR systems may provide limited but compelling haptic (tactile) feedback that simulates the feel of forces, surfaces and textures as users interact with virtual objects. VR systems also include a way of interacting with the simulation. In fully 'immersive' VR systems (BOX 2), movement of the body and the sensory flow of the virtual environment are coupled[10]. Movements of the head and body are often tracked so that the visual experience changes in a way that corresponds to real-world head and body movements.

Miniaturization of VR technologies and their growing affordability are helping to address some common criticisms of VR for neuroscience research (BOX 3). As technology continues to improve, the barriers to widespread adoption of VR are constantly diminishing.

Why use VR?

The use of VR in neuroscience research offers several unique advantages. First, and perhaps most importantly, VR allows naturalistic interactive behaviours to take place while brain activity is monitored via imaging or direct recording. This allows researchers to directly address many questions in a controlled environment that would simply not be possible by studying performance 'in the wild'. Second, VR environments allow researchers to manipulate multimodal stimulus inputs, so the user's sensorimotor illusion of being 'present' in the represented environment is maximized (BOX 2). By providing realistic stimulation to multiple sensory channels at once, VR engages the sensorimotor system more fully than the simple stimuli used in most

Box 1 | **Anatomy of a virtual environment**



a zSight HMD by Sensics

b HMD with optical see-through by Trivisio

c Monocular HMD by Liteye Systems

d

There are key technical components that are found in most virtual reality (VR) systems. The most commonly used forms of sensory stimulation are visual displays (see the figure). Stereoscopic vision is accomplished by presenting horizontally displaced images to the left and right eyes, mimicking the natural disparity in visual images registered by each eye owing to horizontal displacement in the head. The brain treats computer-generated images as any other optical input, fusing the images to create a sensation of three-dimensional space. The perspective from which a viewer experiences the computer-generated image is controlled by a virtual camera (unseen by the viewer). Changing the location or direction of the camera changes the view, as does viewing the world through a real camera. To ensure that viewpoint changes according to where the user is looking, it is necessary to track the location of the user's head. The images can be delivered either by a closed (personal) head-mounted display (HMD; parts **a**–**c** of the figure) or by an open display such as a computer monitor or projection screen (part **d** of the figure). HMDs may be more immersive, but open displays are often easier to engineer and work with (although HMDs are becoming highly compact and affordable).

Auditory stimulation is commonly used in conjunction with visual display, often in the form of realistic three-dimensional spatial surround sound. Haptic (tactile) feedback is sometimes provided using devices called tactors — actuators that vibrate against the skin or within input devices. Haptic feedback devices are increasingly able to deliver a strikingly compelling sense of physical contact with the virtual world[115]. The real power inherent in virtual environments, however, is their ability to present synchronized simulations to multiple sensory channels[116].

Interactivity is another key component of VR. Immersive VR environments incorporate highly sensitive head- and body-tracking systems. Sensors monitor the user's position to provide an egocentric reference frame for the simulation (that is, a first-person perspective). A popular approach is inertial tracking, which uses accelerometers that behave in a similar way to the vestibular system (accelerometers are electromechanical devices with moving parts that use gravity to detect orientation, movement and vibration and then send this information to a computer). Inertial tracking also uses gyroscopes for maintaining orientation and magnetometers for maintaining accurate direction information. Other tracking alternatives make use of cameras, changes in the magnetic field orientation of a body-worn sensor, changes in the time taken to receive an ultrasonic frequency by a body-worn sensor, or some hybrid of these.

Less immersive means of retrieving input from users include common keyboard, mouse and joystick devices. Although these control devices are easy to work with, naturalistic user interfaces that replicate real-world interactions (such as reaching, grasping or pushing) are becoming the norm.

psychological research, increasing the potential to elicit realistic psychological and behavioural responses.

VR also offers maximal control over multisensory stimulation. This kind of control is beneficial for understanding sensorimotor interactions between, for example, proprioception and visual experience (that is, interactions between brain regions responding simultaneously). In some studies, parts of the represented world are transformed between eye saccades to explore how consciousness retains models of the world while engaged in action[11].

VR also increases the role of motor activation during simulated experience, as users can move through and physically interact with virtual objects. Virtual environments can present combinations of stimuli that are not found in the natural world and researchers can execute changes in the environment that would not be possible physically. VR might be used to decouple visual and vestibular sensation, revealing the roles of separate brain systems that are usually enlisted simultaneously (for example, postural responses may reflect input from visual perception more than from motion perception, or vice versa).

Last, the equipment used to create interactive simulations is readily leveraged for fine-grained recording and analysis of behavioural responses that can be used to monitor or produce change over time. In immersive VR, tracking devices affixed to the head or hands sample the wearer's body coordinates in space very rapidly, and this information can be recorded and analysed to assess very minute improvements or changes in muscle control over a period of time. For basic neuroscience researchers, multisensory stimulation and embodied interaction are difficult or impossible to achieve otherwise. Likewise, practitioners such as clinical and rehabilitation therapists gain unique benefits from being able to control stimuli in VR environments and gather data on patients' responses (for example, they can create environments that stimulate phobic responses).

In the next section we review the contribution of VR systems to various areas of neuroscience, including spatial cognition, social cognition and other research domains.

Experimental domains

VR environments meet the needs of several research domains related to cognition and perception, and VR environments have been created for studies in both humans and animals. In this section, we highlight several areas in which VR has become an established part of research instrumentation and methodology.

Spatial cognition and navigation. VR environments enable researchers to study human navigation traits using tasks that are directly comparable to those that have been used in animal research for many years. Before the advent of VR, researchers were forced to seek alternatives (for example, mental rotation or map learning) to these tasks in order to relate human brain activity to results from animal studies. VR's compatibility with functional MRI (fMRI) further encourages explorations inspired by neuroscience research in animals.

An environment that has long been used in animal spatial cognition research is the radial maze. Analogous research in which humans navigate a virtual radial maze reveals evidence for hippocampal activity (as expected from animal studies), but also evidence of frontal cortex activity, suggesting the additional contribution of working memory circuits[12]. Similar work using a virtual water maze confirms the involvement of areas that are external to the hippocampus (for example, the parahippocampal gyrus, precuneus and fusiform)[13]. Such studies would not have been feasible without VR. With VR, matching environments and tasks can be used for animal and human studies even when they differ in scale or mobility.

VR systems also allow researchers to rapidly change or eliminate landmarks or pathways. This is used in many studies to probe what was learned during navigation. For example, landmarks such as distant buildings or other environmental cues can be altered to explore how users rely on them to navigate.

Virtual mazes have proven useful in identifying distinct navigation strategies, along with their underlying neural substrates. Two prominent strategies have emerged using a virtual radial maze with recognizable features and patterns on outside walls[14]. 'Spatial' learners rely on relationships between identifiable landmarks — such as the patterns on the wall of the environment — to form a cognitive map. So-called 'response' learners use a non-spatial strategy, remembering a series of turns at each decision point (for example, counting the turns and directions without forming a cognitive map). In this work, neural data revealed patterns related to the virtual behaviour. Spatial learners exhibited more hippocampal grey matter compared to response learners, whereas response learners exhibited comparatively more caudate nucleus grey matter. In this case, landmarks were removed from view and maze pathways were altered to probe for navigation deficits belying each strategy for navigating the space.

A virtual Morris water maze has been used to demonstrate age-dependent differences in navigation strategy. In the (physical) animal version, rats dropped into a water tank use the patterns on the walls to find, swim to and remember the location of hidden platforms under the water. With a (virtual) human equivalent, researchers find that the time to locate a hidden platform increases with age, and that young participants spend more time looking in the correct location for a previously learned target than older participants[15]. A related study, using a similar task, found that hippocampal volume positively correlates with performance differences in young but not old participants[16]. The authors speculate that older participants may compensate for lack of hippocampal contribution by adopting a non-spatial strategy that relies more on the caudate nucleus and prefrontal cortex.

Spatial cognition researchers have also used VR with patient populations. For example, patients with

Box 2 | Immersion and presence

When considering the technical components of virtual reality systems, it helps to distinguish between the concepts of 'immersion' and 'presence'[117]. Immersion, sometimes called sensorimotor immersion, refers to the degree of physical stimulation impinging on the sensory systems and the sensitivity of the system to motor inputs. The level of immersion is determined by the number and range of sensory and motor channels connected to the virtual environment, and the extent and fidelity of sensory stimulation and responsiveness to motor inputs (for example, head and body movement, and hand gestures to make commands). Immersion can be increased by: increasing the range of visual stimuli, such as the amount of visual field engaged and the fidelity of visual displays; providing three-dimensional spatialized sound, such as sound that is fixed around a moving body; using interfaces with a tight sensorimotor coupling for which changes in sensory stimulation respond naturally to body movements, such as head, hand and other motions; and through other techniques that increase the sensorimotor realism of objects and settings in the virtual environment.

The psychological product of technological immersion is presence — the psychological sensation of being in the virtual environment instead of the physical environment and interacting with media. A commonly cited definition of presence is "the perceptual illusion of nonmediation"[118], but it is often simply described as the sensation of 'being there' in the virtual space[117]. Although commonly measured by self-report, researchers have begun looking for physiological indicators of a user's degree of presence. For instance, placing a person in a virtual situation that is known to be stressful (for example, a high place) leads to bodily responses similar to those expected in a real-world analogue, such as increased heart rate and skin conductance, and decreased skin temperature[119].

Morris water maze
A classic experimental paradigm used to assess spatial navigation abilities. Traditionally, an animal swims around a pool for a number of trials, freely exploring the space. In later trials, the goal is to find the fastest route to a submerged platform.

Place cell
Hippocampal cell that encodes different components of the relationships between spatial locations.

Huntington's disease (who are characterized by degraded caudate function) have shown a compensatory increase in hippocampal activity during tasks that are normally associated with caudate activity, so that their observable navigation behaviour appears normal[17]. In patients with epilepsy[18], post-surgery lateralization of medial temporal lobe (MTL) activation is determined by the side of pathology (for example, patients with right-side MTL epilepsy showed increased left-lateralized hippocampal activation during a VR navigation task) rather than by gender, as suggested by studies of healthy subjects[19].

VR systems can also be used in conjunction with invasive recording of brain activity. This has been invaluable for demonstrating human place-cell activity. Although neuroimaging studies suggest that humans may have place cells that are analogous to those reported in animal studies, this is difficult to verify because hippocampal and parahippocampal regions respond to both visual stimuli and to specific locations. Directly recording from neurons in MTL and frontal lobes to separate the input of these factors using VR[20] reveals human place-cell activity specifically related to navigation (see also REFS 21–23 for similar work using electroencephalography (EEG) to measure theta activity).

Finally, studies on gender differences, a popular topic among navigation researchers, have also benefited from the use of VR with fMRI scanning. There is evidence of increased activation of the posterior cingulate/retrosplenial cortex in males while navigating a virtual environment[24]. The cingulate/retrosplenial cortex may have a role in our ability to orient ourselves in space. However, females were shown to demonstrate relatively more activity in the parahippocampal gyrus, which has been linked to our ability to identify and remember landmarks. These findings coincide with suggestions that females make relatively more use of landmarks than men do during navigation.

Spatial navigation systems for animals. Animal studies also inform our knowledge of spatial cognition and navigation. Organisms with simpler nervous systems, such as bees and ants, must navigate space to survive (for example, to remember the location of food or to avoid predators and other dangers). Understanding how insect neural substrates handle navigation problems using landmarks, path integration or possibly even some form of cognitive map formation can shed light on necessary and sufficient informational and cognitive processing requirements. Creating virtual environments in which animals behave as they do in the real world and that allow researchers to study variables such as smells, sounds or sights has been a technical challenge. Here we review some of the progress that has been made towards a new era of VR systems with hardware and software that has been designed for animal research.

Virtual environments have been used to study flight control in both tethered and untethered insects (FIG. 1). Recent work details the design of a VR system in which tethered moths are presented with visual information on a small, dome-shaped rear projection screen[25]. Along with visual information, olfactory stimulation in the form of female pheromone is provided to induce changes in flight direction (inferred from adjustments in wing shape and abdomen movements for ruddering). In open-loop studies (in which the experimenter controls the visual stimulation as well as the pheromonal stimuli independent of insect behaviour), visual display changes had the greatest effect on wing responses. When the experimenters changed the visual information to indicate to the animal that it was veering away from a straight flight path, it would adjust its wing pattern and abdominal position to compensate and correct its flight path. In closed-loop conditions (for example, where the insect's wing and abdomen responses to visual stimuli drive the simulation display), abdominal movements produced changes in visual heading (that is, direction of flight) and orientation with respect to the ground.

Some researchers argue that untethered flight is often more appropriate for insect navigation studies because mechanosensory feedback provided by specialized balance organs is undermined by the tethered approach[26]. To this end, these researchers have designed a small

Box 3 | Common criticisms of virtual reality

Early virtual reality (VR) equipment suffered from many inadequacies, such as being large and unwieldy, difficult to operate and very expensive to build and run. Early experiences with these systems may have soured public enthusiasm for VR, and have led to a range of criticisms that are likely to have slowed adoption. Nevertheless, researchers have steadily progressed in making VR hardware and software more reliable, cost effective and acceptable in terms of size and appearance.

Cost
The cost of advanced VR systems remains relatively high. For example, a wide-field-of-view head-mounted display (HMD) can cost tens of thousands of US dollars, a tracking system capable of covering a large area can cost upwards of a hundred thousand dollars, and exploratory new systems can cost millions to develop. Nevertheless, the trend follows that of computer equipment in general towards a rapid decrease in size and price, and an increase in computational power and ease of operation.

Requirement for specialist technology skills
Creating virtual worlds and characters continues to require specialized skills in three-dimensional modelling, texturing, character animation and programming. However, increasingly powerful tools are becoming available — some at no cost — that simplify these tasks. Furthermore, large repositories of object and character models are available, and programming environments for inserting these models into VR systems are becoming easier to use. Finally, creating interactivity is also becoming easier thanks to visual programming and scripting languages (such as Virtools and Vizard).

Bulkiness of equipment
The earliest incarnations of VR used HMD helmets that engulfed the user's entire head and face, and weighed several pounds. This problem has steadily diminished thanks to progress in the design of HMDs (some are approaching the size of an ordinary, albeit heavier, pair of sunglasses).

Cybersickness
A lingering concern for users of VR is simulation sickness, or 'cybersickness', which acutely threatens the widespread adoption of VR for therapeutic or training applications requiring repeated use over time. Some users are reported to experience nausea after using VR. A widely accepted explanation for this is the incongruity between sensory inputs: as visual information provides users with the sense of motion, vestibular feedback can indicate a degree of movement that is not matched by vision. Although this continues to be a problem, some potential sources of cybersickness, such as a lag between the timing of tracked movements and updating of computer-generated imagery, are being eliminated with technical advances. However, some cybersickness may persist when aspects of stimulation from the physical environment, such as gravitational or inertial force, remain in conflict with what is being experienced in the virtual environment (for example, flying in a plane).

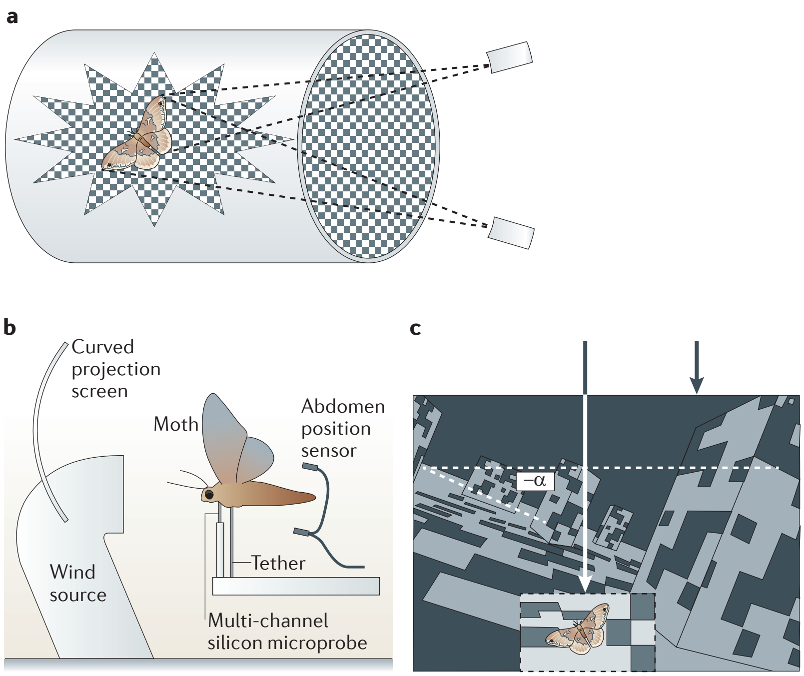


Figure 1 | **Virtual reality environments for studying insect navigation.** Virtual reality (VR) environments for animals contain the same essential components as VR systems developed for humans (BOX 1). Sensory stimulation must be provided while the animal's location is tracked in space (at least for closed-loop simulations where the animal's behaviour influences the displayed information). This figure shows specialized chambers for studying insect navigation. **a** | A cylindrical enclosure that allows untethered flight. The sides of the chamber are covered with light-emitting diodes that display changing patterns to the insect's compound eye. The insect's location is tracked with cameras, and the direction of flight can be influenced by releasing a puff of odorant (for example, female pheromone) into the chamber. **b** | A tethered insect in front of a curved rear-projection screen. **c** | The geometric shapes displayed to the animal on the screen. The animal 'flies' around the space and adjusts its wing and abdomen positions to change course or to avoid the virtual obstacles. Part **c** is modified from REF. 25 © (2002) Elsevier.

flight arena equipped with light-emitting diode (LED) visual displays, olfactory stimulation and motion tracking[26,27]. Regardless of whether the insects are tethered or untethered, the results from these studies demonstrate that insects respond to these virtual environments in ways that match their behaviour in the real world, implying that they perceive these virtual stand-ins as in some way equivalent to the natural environment.

The navigation skills of small mammals is also increasingly studied using specially tailored VR systems. For instance, a 360 degree enclosure that is totally isolated from smells, sounds and external visual information can be used to stimulate visual, olfactory and proprioceptive pathways in rats and mice[28]. It can likewise distort what is normally experienced, so that environmental context can be enriched or impoverished on demand. Virtual stimuli may change the behavioural or biochemical condition of the organism, which can be measured during or after an experimental session.

Researchers have described a VR system used to study mouse navigation that promotes similar cell firing rates and spike timings to those recorded in real environments[29]. The system includes a spherical treadmill on which the head-stabilized animal runs, while a visual display is projected onto the inner portion of a curved screen. These researchers use this VR setup in conjunction with subcellular-resolution microscopy to examine hippocampal place-cell activity[30]. The authors report finding signatures of place fields as the animals moved along a virtual linear track, including asymmetric ramp-like membrane depolarization and increased amplitude of theta oscillations. These results lend empirical support to a 'soma–dendritic interference' model positing excitatory dendritic input and inhibitory input near the soma.

In summary, spatial cognition and navigation research shows the benefits of using VR for stimulus presentation. Interactive virtual environments have enabled us to study human navigation in behavioural and neural contexts simultaneously, and to rapidly make changes to environments to explore a host of theoretically important questions in both humans and animals.

Place fields
Populations of hippocampal place cells that enable the formation of spatial memories. Collectively, these 'fields' enable the encoding and recall of complex spatial relationships.

Multisensory integration. Virtual environments are designed for multimodal sensory stimulation, making them ideal for multisensory integration research (for example, binding disparate inputs such as sight, sound and touch into a unified perceptual experience).

This multimodal stimulus capacity is exemplified by research on the body-transfer illusion. The perceptual integration of multimodal information that arrives simultaneously at our sensory organs is vital to our perception of the world and of ourselves. Although we experience our sense of self as a stable, durable percept, this experience is actually surprisingly modifiable, suggesting continual updating of our perception of bodily and conscious state. This is strikingly demonstrated by the effect known as the body-transfer illusion[31], which has classically been demonstrated by the rubber-hand illusion[32]. When a rubber hand (visible in the position normally occupied by our actual hand) and our actual hand (hidden from view by a screen) synchronously receive touch feedback (that is, we feel stroking on the real hand and simultaneously see it on the rubber hand), participants begin to experience the sensation that the imposter limb is part of their own body.

Several researchers have used VR to demonstrate a full-body version of this effect[33,34]. Initial studies used simple displays to show participants a stereoscopic view of their own video-recorded body displaced spatially from its actual position (effectively changing their perspective from first to third person). Synchronous visual and tactile feedback led participants to indicate (through questionnaire responses or physiological measures) a sense of ownership over their spatially displaced self.

More recent work has shown the power of VR by using more elaborate virtual worlds in which participants control, observe and interact with computer-generated avatars[31]. This technique enabled the researchers to analyse which variables are important for the body-transfer illusion and to compare their results with studies that used less-sophisticated stimuli. By manipulating perspective (first versus third person) as well as the timing of visuotactile stimulation (synchronous versus asynchronous), they were able to determine that a

Binding problem
The integration of sensory cues and information in higher-level cortical regions underlies cognition and consciousness. Binding requires large-scale synchronization of cortical activity to create a unified perceptual experience.

Theory of mind
The ability to empathize with another individual. It involves the tendency of humans to attribute mental states — such as goals, beliefs and knowledge — to another individual that are in some way analogous with our own mental state.

Mentalizing
Mentalizing is the process of interpreting the intention of others, allowing one to anticipate the behaviour of objects and individuals.

first person perspective is key for obtaining the effect, whereas visuotactile synchronicity might actually be dispensable.

Multimodal stimulus control is also important for inducing a sense of 'presence' (BOX 2) in virtual environments, which is believed to be of crucial importance for the effectiveness of VR training in medical, military and other educational simulations, as well as for therapeutic applications in which users respond to environments that simulate troubling situations from the physical world. The value of multimodal control has been demonstrated in studies showing that combined visual and proprioceptive feedback leads to a stronger sense of presence than using a joystick to control responses[35,36]. VR's multimodal stimulus capabilities may ultimately shed light on the binding problem, as researchers have found that the precisely coordinated synthesis of separate sensory input channels is necessary to achieve and maintain a sense of presence.

Social neuroscience. VR allows imaging of brain activity during naturalistic, face-to-face social interactions, and has shed light on the interpretation of biological motion cues, theory of mind development and responses to displays of distress.

For example, a series of VR studies has helped to identify brain regions that are involved in interpreting others' face and eye movements[35,36]. Participants approached by a virtual character exhibiting an angry expression consistently display activation of the superior temporal sulcus (STS), as well as the lateral fusiform gyrus and a region of the middle temporal gyrus. Similar results have been reported for judgements of gaze avoidance or engagement.

This research has potential for providing an understanding of the theory of mind deficit that is thought to occur in autism spectrum disorders[37]. For example, in normal controls, when a virtual other shifts gaze in an unexpected direction (for example, looking in the opposite direction of a suddenly appearing virtual object) the result is increased right posterior STS (pSTS) activation. In children with autism, however, there is no difference in activation between expected- and unexpected-direction shifts. These findings highlight the importance of the pSTS for interpreting others' intentions, and could ultimately prove valuable for treating children with autism. VR's high ecological validity is an asset to such potentially translational research.

The interactive realism of VR also aids research on mentalizing. In such studies, participants normally respond to stories, cartoons or movies about others, and the simple, repetitive tasks that are typically used are very different from the spontaneous, occasional mentalizing we do in real life[38]. Combining VR with brain imaging allows the examination of brain activity during spontaneous mentalizing. For example, in a taxi-driving task, participants were made to ferry unseen passengers to various destinations in a virtual replica of London. Subjects responded to audio cues from customers along with other irrelevant audio cues, and they also had to interpret the behaviour of visible others on the street (for example, people about to cross the street and cars moving in traffic). During mentalizing events (regardless of whether considering the intentions of the unseen passengers or the visible others on the street), the authors consistently found increased right pSTS activation. During events involving visible others, they also found medial prefrontal cortex (mPFC) activity. The authors suggest that the pSTS might be involved not only in detecting bodily cues of intent but also in analysing the goals of that behaviour, whereas the mPFC may be involved in predicting future actions of visible others. This combination of realistic mentalizing and fMRI would have been unfeasible before the advent of virtual environments.

VR also enables researchers to ask questions that might otherwise be limited by ethical concerns. For example, VR has been used to replicate the famous obedience study of Milgram, complete with palpable distress on the part of participants tasked with 'shocking' virtual confederates[39]. This result begs the question: why would participants be averse to supplying virtual shocks to non-existent people? A replication of the Milgram study in conjunction with fMRI sheds light on whether behaviour is related to empathic concern for the virtual character, or rather is based on personal distress created in the participant by the sight of another in pain[40]. Although they did find activation in areas known to be involved in affective processing, the researchers found no activation in the anterior cingulate cortex and insula — areas known to be associated with empathic response. This result suggests that observing a virtual other in distress creates personal discomfort for the observer, rather than empathy for the virtual character. This of course does not necessarily imply a similar response to pain in the original Milgram study. Prior studies have reported evidence of activation of cortical pain centres during the observation of real faces expressing pain[41].

Finally, a recent application of VR involves 'hyperscanning' — observing the interaction of more than one participant as they are each being scanned by a separate fMRI system. Thus, hyperscanning allows researchers to measure the reactions of multiple participants — each within their own imaging system — to shared social situations in a VR environment. This approach has been applied to neuroeconomics research using participants in separate fMRI scanners[42]. The authors find periods at various points throughout the task when regions of each brain are active at the same time (coherent activation) across subjects. Scanning each individual separately as they perform a task would require identifying observable events in the task environment that can be used to locate synchronized neural responses between participants during analysis. But responses to environmental events are often too weak to be identified in the data (for example, when interacting participants are trying to predict each other's behaviour), making it likely that several periods of activation coherence across participants will be missed. The possibility of using internet-connected virtual interactive scenarios in which several subjects can carry out interactive tasks while in scanners at distant locales makes the use of VR particularly attractive for this kind of research.

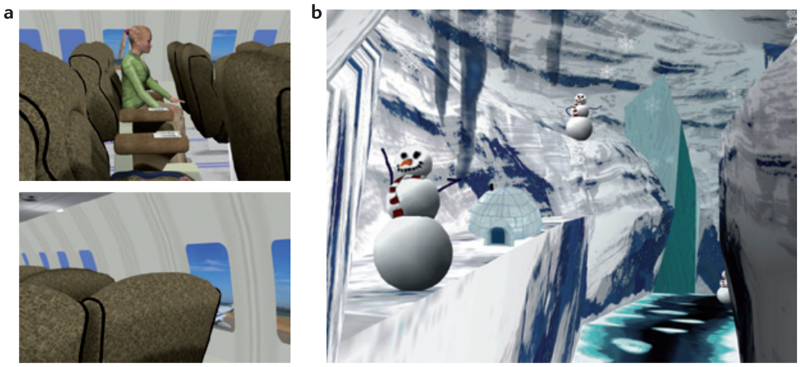


Figure 2 | **Examples of virtual environments for therapeutic application.** **a** | An example of a simulation used in exposure therapy to treat fear of flying. This type of simulation allows observers to experience the sensation of flying in a commercial jet, including turbulence and landing, from a first-person perspective. Other examples include simulations for acrophobia, public speaking and cue reactivity (reaction to drug-related environmental cues). **b** | A simulation used in pain remediation. Specifically, it has been applied to burn victims for distraction to reduce the pain of bandage changing. A user navigates the environment, which is designed to conjure thoughts of cold, during treatment. The distraction created with this simulation has yielded impressive pain reduction results, over and above the pain reduction produced by opioid pain medications. Image **a** is courtesy of WorldViz. Image **b** is courtesy of Stephen Dagadakis © Hunter Hoffman (Worldbuilding by Jeff Bellinghausen and Chuck Walter, Brian Stewart, Howard Abrams and Duff Hendrickson).

Therapeutic applications

In addition to basic research into brain function, several researchers have demonstrated the effectiveness of VR for therapeutic applications. VR has successfully been applied in at least three domains: psychiatric disorders, pain management and neurorehabilitation. VR offers some distinct advantages over standard therapies, including precise control over the degree of exposure to therapeutic scenarios (for example, treating fear of flying without requiring patients to fly in a plane), the possibility of tailoring scenarios to individual patient needs, and even the capacity to provide therapies that might otherwise be impossible. For example, one team has included artefacts and images that are directly related to a person's past inside virtual environments[43].

Psychiatric disorders. VR offers a controlled user experience that is akin to dosage control in psychiatric treatments, along with a potentially high degree of realism to bolster the transfer of results to the real world (FIG. 2). VR treatment has been applied to a range of disorders, including fear conditioning[44], anxiety disorders[45] and brain damage[46].

One of the most widely explored applications of VR to psychiatric rehabilitation is in the area of phobia treatment. Phobias are commonly treated with exposure therapy, which systematically introduces a feared object or situation to the patient, beginning with a small 'dose', such as imagining the phobic stimulus, and graduating to more anxiety-provoking situations. Over time, the patient may gain a sense of control over the environment and thus over their fear. VR has the potential to solve many problems that are common to real-world exposure therapy and has generally produced favourable results[19,47]. The virtual environment permits therapists to adjust the degree of exposure and attain a high level of consistency across sessions. In addition, therapy involving real-world exposure (for example, handling real spiders) is simply not an option for some patients. Simulations may also provide easier access to difficult-to-arrange real-world situations (such as airplane flights, or facing animals or large audiences).

Several studies have compared outcomes from real-world and VR exposure therapy for acrophobics[43,48,49] using real locales (for example, a rooftop or balcony) and VR equivalents[43,48,49]. Although overall anxiety was slightly lower in virtual environments, the amount of decline in anxiety from pre- to post-test was similar for real and virtual locales. Studies of VR exposure treatment for other phobias, such as arachnophobia[45,47], fear of flying (aviophobia)[50,51], agoraphobia[52–54], claustrophobia[45,47] and fear of public speaking (glossophobia)[47,55], have produced similar results[47]. It remains to be seen whether VR will ultimately be able to produce the stress levels — and improvements in patients' phobias — that are equivalent to those produced by real-world exposure therapy; however, currently available VR may be a valuable therapeutic starting point for those who are unable to withstand the greater stress of real-world exposure therapy.

VR therapy has been compared with another common type of therapy — imaginal exposure — in patients with a fear of flying[56,57]. A major problem with imaginal exposure is that not all patients can imagine the stressful situation realistically enough to inspire high anxiety. In these studies, VR was found to aid in recreating the psychological experience of flying, and patients experiencing VR exhibited more anxiety and a correspondingly greater decline in anxiety over time than patients undergoing imaginal therapy.

Imaginal exposure therapy is also used to treat post-traumatic stress disorder (PTSD), subject to the same limitations described above. In a case study of PTSD brought on by exposure to the terrorist attacks of 11 September 2001 (REFS 58,59), researchers found a large reduction in PTSD symptoms in survivors after VR exposure therapy. They report a 90% reduction in symptoms after six (approximately 1 hour long) VR sessions over several weeks. Encouraged by results like these, VR is increasingly being used in hospitals to evaluate soldiers on active duty and to diminish the response to traumatic memories and environments in returning soldiers[60–68].

Pain remediation. One neurological application of VR is to aid analgesia. Virtual environments provide perceptual representations of one's body and the world that can shift the patient's attention and slightly alter the perceived properties of pain[69–72]. VR pain relief results from VR's capacity for multimodal stimulation and interactivity.

For example, consider Ramachandran's famous demonstration of phantom limb pain reduction using a mirror box to provide visual input from the remaining symmetric limb[73]. This provides visual feedback that is analogous to moving the missing limb to a more comfortable position. However, the effect may be limited because sensorimotor signals from the non-amputee side of the brain are activated rather than the disordered signals occurring on the actual amputation side. The problem can be remedied using a VR version of this treatment. By placing location sensors on the limb stump and allowing the patient to move it, the correct side of the brain receives kinaesthetic feedback while the visual system receives feedback of a virtual limb moving to a more comfortable position[74,75].

The sense of 'presence' afforded by virtual environments also seems to underlie effective analgesia. A widely publicized application has been the use of VR for pain remediation in patients with burns. Interacting with a virtual winter terrain (FIG. 2) has reduced subjective pain in burn victims by inducing thoughts of 'cold'[76,77]. It must be pointed out, however, that the results of this pain reduction are limited to the period during which the patient is actually engaged with the VR environment and do not seem to extend beyond this period outside the VR environment. Although not yet widespread, this approach has found application in some hospital settings.

Maximizing sensory immersion and hence one's sense of presence in the virtual environment seems to strengthen analgesic effectiveness. A review of studies of VR pain analgesia for burn victims finds that more highly immersive VR equipment (for example, a high-end head-mounted display (HMD)) corresponds with greater levels of relief[78]. There is little evidence of pain relief when patients view VR stimuli on a computer screen, in monoscopic three-dimensional video or using a limited-field-of-view HMD. Furthermore, the content of the VR simulation must be compelling (for example, virtual scuba diving versus strolling around a virtual room) to be effective for pain relief.

VR's interactivity also has a role. In a recent study, participants either passively watched video game footage through an HMD or actively played the game while experiencing a cold pressor to induce discomfort[79]. Those actually playing the game were able to tolerate higher levels of discomfort. Both immersion and interactivity have the effect of increasing presence, and indeed several researchers have demonstrated that increased presence correlates with more effective pain relief[80–82].

Neurorehabilitation. Neurorehabilitation applications have been focused on two areas: balance disorders and their underlying multisensory integration mechanisms[83,84], and recovery of function after stroke[11,41,85,86]. VR simulations can be highly engaging, which provides crucial motivation for rehabilitative applications that require consistent, repetitive practice. Furthermore, the tracking systems used in VR provide an excellent tool for recording and following minute changes and improvements over time. Indeed, immersive multimodal VRs that link head, hand and body movement to changes in visual and auditory stimuli have proven useful for the recovery of motor function and postural stability[83,84,87,88].

The timing of multimodal stimulation has been linked to recovery from postural and gait disorders. Several studies have shown that postural sway exhibits greater variance with age and in patients with balance disorders. Selective modification of one or more sensory channels has been found to reduce the amount of variance exhibited. This has been done by presenting selectively timed tactile and visual motion cues. Specifically, training with synchronized haptic, auditory and visual cues has been shown to foster reductions in unintended postural sway over trials, particularly in patients with acquired brain injuries, such as stroke[89]. There is evidence that VR helps to engage primary and secondary motor areas related to recovery of muscle control after stroke[90,91].

Similar studies have examined children with gait disorder due to cerebral palsy[92]. After walking on a track while observing a virtual tile floor for 20 minutes, participants showed improvements in walking speed and stride length, particularly those with the lowest baseline speed and stride lengths (as measured before the VR task). Similar trends have been reported for patients with gait disturbances related to multiple sclerosis[93]. Again, the results seem to indicate that the timing of multimodal stimulation in VR (seeing a virtual tile floor under foot while hearing footsteps on the floor) provides feedback that helps the patient to understand that they are currently walking steadily, and helps the brain to bypass damaged areas to some extent in those cases where the sensorimotor vividness of the environment engages reflexive responses.

VR has also found promise in stimulating the recovery of function in patients who have suffered a stroke. To interact with the virtual environment, patients were given a force-feedback-enabled data glove (containing an exoskeleton of computer-controlled finger actuators that modify forces to simulate surface resistance), and after 2 weeks of desktop-VR tasks, improvements in individual finger control, thumb and finger range of motion, and thumb and finger speed were observed[94,95]. These results were retained after a week, highlighting the benefits of VR for rehabilitation. These authors attribute much of the improvement to increased motivation to engage in rehabilitative exercises. The exercises are embedded in a real-world context or a game and can be more engaging than a sterile medical office. Several studies on the use of VR for upper-body exercise with feedback (for example, visual, auditory or haptic information indicating how close a patient has come to a desired performance goal) show significant improvement in the movement, use and control of patients' hands, relative to baseline and to other rehabilitation approaches such as patient-guided exercise and group physical therapy[96,97].

Some caveats. Although the studies reviewed above point to the promise of VR therapy for psychiatric rehabilitation, there are limitations. For one, cost remains an issue. Depending on the situation, an immersive VR system can cost tens of thousands of US dollars, although many of the studies reported here highlight results obtained with commonly available computer equipment. Another problem is the lack of standardization of VR solutions. A more uniform approach to VR system design would probably simplify and speed up the adoption of VR therapies. This problem may soon be resolved, as companies are striving to offer turnkey VR systems. However, perhaps the most substantial problem is the programming requirements for making and modifying virtual environments. This is a major roadblock to widespread adoption, although standardization of VR content would greatly ameliorate the problem, and this situation too is gradually improving.

Although there is healthy growth in the use of VR solutions among researchers, and a growing body of supporting results, members of the mainstream medical community are probably still many years from widespread adoption. This may change once sufficient clinical evidence has been accrued and systems are simple and robust to use. BOX 3 contains a more complete discussion of VR's current limitations.

Connecting the brain to virtual environments

Most applications of VR in neuroscience focus on influencing and measuring changes in brain activity, but another application is the creation of brain–computer interfaces that establish a direct link between the nervous system and virtual environment properties[98]. For example, electrical recordings from the central nervous system and muscle activity can be used to control digital objects (ordinarily done by using a joystick or mouse) in VR.

Brain–computer interfaces range in their degree of invasiveness. Implantable brain–machine interfaces, such as those being developed with non-human primates[99,100] and humans[101,102], use virtual environments as a medium to present movement-related feedback in a closed-loop system (for example, for training primates to reach and grasp virtual objects with a robotic arm and for training quadriplegics to manipulate virtual switches to control aspects of the environment, respectively). Some brain–computer interface developers use EEG to achieve similar results[103]. Recent research has shown that humans have a remarkable ability to learn to focus attention and voluntarily influence activity in MTL neurons (by increasing or decreasing their firing rate) to control on-screen images[104]. These findings may ultimately lead to technologies that respond to user intentions[105].

A primary benefit of linking brains to VR environments is to provide safe practice environments. For example, virtual environments can serve as a surrogate for training patients to use neuromotor prosthetics before attempting to use a new prosthetic in the real world[106].

Recent work aimed at developing methods of studying sensorimotor disorders using a combination of robotic arms, simple virtual environments and fMRI[107] is further bridging the gap between brain–machine interfaces and rehabilitation research. Participants lie in an fMRI scanner and control a plastic robotic arm near their waist, while viewing (on a monitor) graspable virtual objects and the location of the virtual arm. Although the number of papers and applications in this area is increasing, the underlying neuroscientific principles are just beginning to be understood[108].

Conclusions and future trends

As we have discussed, VR makes it possible to examine brain activity during dynamic, complex and realistic situations. In applied domains such as rehabilitation, VR methods continue to accrue validating results. This trend should continue as these methods become widely adopted and are extended to the study of different neuroscience areas and a wider range of therapies.

The future of VR in neuroscience is strongly tied to developments in technology that help to immerse the user in convincing, life-like sensorimotor illusions. For example, panoramic high-resolution HMDs are now available with a field of view greater than 120 degrees (the human field of view encompasses nearly 180 degrees). However, the widespread adoption of VR is likely to involve smaller, less-expensive systems, and will be bolstered by the increasing proliferation of consumer devices.

A likely trend for VR will be towards greater user mobility. This will be valuable for understanding neural activity in 'in the wild' (that is, in the real world) and for understanding the role of the body in cognitive performance (that is, embodied cognition). To this end, a promising variant of VR that lends itself to movement outside the laboratory is known as augmented reality (AR). In AR, the user views the real world through a display (either head-mounted or screen-based) equipped with a position-sensing device and a camera (although some HMDs allow the user to see directly through, rather like a pair of sunglasses). This view of the world is augmented by the addition of computer-generated, location-specific objects and information (that is, digital items are overlaid on the natural environment where and when they are needed). AR may prove valuable for spatial cognition research, as it allows participants to navigate in real-world locales while learning the locations of virtual landmarks and features. These virtual details could easily be removed or changed to evaluate what has been learned. This would also allow researchers to study the contributions of body movement through a space of unlimited size. AR may also prove valuable for rehabilitation. For example, displaying a virtual limb whose movements are to be matched by a patient trying to recover function could allow for incremental challenge and heighten motivation to practice.

Technologies for observing neural activity while the subject is mobile currently exist. For example functional near-infrared imaging (fNIR) is an evolving technology that, like fMRI, measures cortical activity; however, whereas fMRI requires a strong magnet, fNIR relies on beams of light, making it small and mobile. Near-infrared light is delivered to the surface of the scalp, and light scatter varies depending on oxygenation level in the assessed regions, providing an indirect measure of neural activity. Although limited to a few centimetres of cerebral cortex, and not as precise as fMRI, fNIR is promising for brain–computer interface technology, as well as for use in adaptive training simulations that adjust to the user's cognitive or emotional state in real time[109]. In addition to fNIR, EEG systems can be used in mobile contexts. In fact, several companies have developed wireless EEG systems for use in brain–computer interaction applications (for example, wheelchair control or video-game control). These systems are very inexpensive and may prove robust enough to be used in a variety of research applications (for example, brain–computer interface development). However, the precision of these devices is currently an open question.

Other likely developments include improvements to sensory displays that have lagged behind visual and auditory displays, including displays for taste, smell and touch. This area has received limited attention over the past 20 years[110–112], with many challenges still ahead[113]. However, research in this area is on the rise. For example, researchers are currently working on a head-worn system that can supply smell and taste to the audio-visual experience, potentially creating a new level of immersion and presence[114].

Overall, the trend appears to be for computer-generated media and consumer devices to become more like the VR systems once found only in advanced VR and simulation laboratories. As these software and hardware components become ubiquitous, VR may increasingly be viewed as an ordinary part of neuroscience research and therapy.

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FURTHER INFORMATION
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