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Multipurpose Virtual Reality Environment for Biomedical and Health Applications

Jordi Torner, Stavros Skouras, José L. Molinuevo, Juan D. Gispert, and Francisco Alpiste

***Abstract*—Virtual reality is a trending, widely accessible, and contemporary technology of increasing utility to biomedical and health applications. However, most implementations of virtual reality environments are tailored to specific applications. We describe the complete development of a novel, open-source virtual reality environment that is suitable for multipurpose biomedical and healthcare applications. This environment can be interfaced with different hardware and data sources, ranging from gyroscopes to fMRI scanners. The developed environment simulates an immersive (first-person perspective) run in the countryside, in a virtual landscape with various salient features. The utility of the developed VR environment has been validated via two test applications: an application in the context of motor rehabilitation following injury of the lower limbs and an application in the context of real-time functional magnetic resonance imaging neurofeedback, to regulate brain function in specific brain regions of interest. Both applications were tested by pilot subjects that unanimously provided very positive feedback, suggesting that appropriately designed VR environments can indeed be robustly and efficiently used for multiple biomedical purposes. We attribute the versatility of our approach on three principles implicit in the design: selectivity, immersiveness, and adaptability. The software, including both applications, is publicly available free of charge, via a GitHub repository, in support of the Open Science Initiative. Although using this software requires specialized hardware and engineering know-how, we anticipate our contribution to catalyze further progress, interdisciplinary collaborations and replicability, with regards to the usage of virtual reality in biomedical and health applications.**

***Index Terms*—Motor rehabilitation, neurofeedback, virtual reality.**

I. INTRODUCTION

VIRTUAL reality (VR) environments have been in use in training applications, for over four decades. In recent times, the active development of 3D technologies concerned with medical therapy, training and rehabilitation has become increasingly important as an area of interest in research and healthcare. Moreover, biomedical applications using the VR technology are receiving increasing attention and are becoming increasingly accessible to consumers [1], [2]. User studies show that such applications are both effective and intuitive [3], [4].

From the invention of stereoscopy in 1844 [5] to its first industrial application in flight simulators for training pilots in 1981 [6], VR has followed a very interesting technological history, reliant on a series of independent engineering innovations [5], [7]–[11]. At present, VR is a technology that uses smartphones or specialized headsets in combination with physical spaces or multi-sensory environments, to generate realistic images, sounds and stimuli that simulate the user's physical presence in an artificial space. VR offers users the possibility to experience psychological states of immersion and involvement and gives rise to a sense of presence, even in physically impossible situations. In the most advanced contemporary VR applications, the user experience is enhanced by the technological capacity to map physical movement into the VR environment through the use of accelerometers and other movement-sensing devices, as well as by the addition of other innovative features that complement a multi-sensory immersive experience (e.g. stimulation via temperature changes or olfactory information, manipulation of proprioceptive state via mechanical floors, monitoring of brain activity via neurofeedback, etc.).

II. RELATED WORK

Due to the relative accessibility of VR and due to its capacity to provide an experience with high ecological validity, compared to other laboratory technologies, VR has been used in a variety of biomedical and healthcare applications. Such applications range from psychiatric treatments to rehabilitation and from medical education to surgical training. Notable examples of psychiatric applications include the treatment of phobias [12], the training of emotion regulation [13] and the training of social skills in autism [14]. Additionally, immersive technologies have been used to support cognitive

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training in older adults with mild cognitive impairment or dementia [15]. VR training can be effective in improving global cognition, specific cognitive domains and psychosocial functioning in people with mild cognitive impairment [16] and dementia [17], including dementia due to Alzheimer's disease [18]. VR games in which the goal is accomplished by activating specific muscles, thereby facilitating rehabilitation physiotherapy [19], [20], comprise another good example of the rapidly expanding field of "serious gaming" using VR [21], [22].

In the field of surgery, in cases of complex operations, tools have been developed to maximize the probability of a positive outcome. VR applications can enable better vision and increased control [23]. Simulations of surgical procedures have been used in training for laparoscopic, robotic, gynecological, neurological and cardiac surgery [24]. In medical education, information on a disease can be directed to different groups (doctors, students or families) and learning is facilitated via first-person perspectives in immersive, realistic environments [25]. Among numerous other applications, VR has been utilized successfully in the rehabilitation of patients with stroke [26]–[29]. VR has been used in neurorehabilitation to help children with attention deficit hyperactivity disorder (ADHD), autism and cerebral palsy [30]. Neuro-rehabilitative therapies that focus on motor recovery have utilized electroencephalography and brain–computer interfaces featuring 3D virtual avatars for controlling simulated movement [31], leading into the field of Virtual Reality Control [32].

Despite the merits of VR and it's extensive utility, most previously implemented VR environments have been tailored to a single application or situation and have not been designed in a way that facilitates modifiability and adaptability to new settings. Here, we introduce the concept of a 'multipurpose VR environment', as a scenery that is prepared in virtual reality that can be readily used to implement a variety of different scenarios and experiences, as well as flexible possibilities for interfacing with real-time analyses, thereby enabling applications for multiple purposes. We then present two representative examples that show distinct possibilities enabled by our open-access work, particularly focusing on contrasting examples where: a) data acquisition and analysis are continuous and at high frequency (100 Hz), yet triggering virtual steps one at a time, for physical rehabilitation purposes; b) data acquisition and analysis occur within a lower time resolution (approximately every 4 s), yet trigger modifications of velocity in discrete intervals (associated with multiple virtual steps), for neurofeedback training purposes.

We have developed a new, open-source VR environment that is suitable for multipurpose biomedical and health applications. This VR environment emulates an immersive (first-person perspective) run in the countryside, in a graphical environment with various salient features (e.g. a lake, a bridge, trees and mountains, etc.; Fig. 1). Two applications have been tested: one in the context of motor rehabilitation following leg injury and another in the context of neurofeedback with real-time functional Magnetic Resonance Imaging (rt-fMRI). These particular applications were motivated by the societal challenges they can address, along with previous reports of successful VR-facilitated motor rehabilitation [4], [19] and successful self-regulation of brain function using VR to represent changes in brain activity [33], [34].

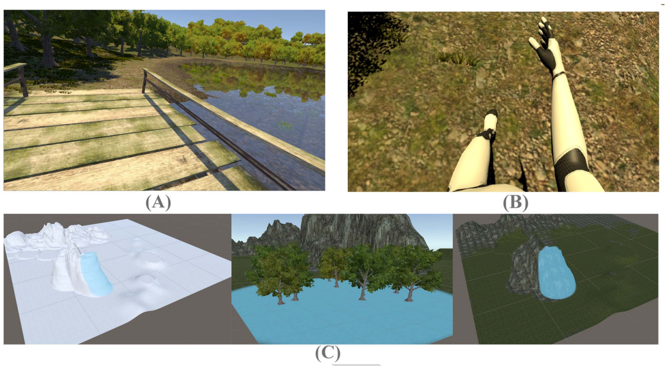

Fig. 1. The designed VR environment. An instance of the landscape typically seen by participants (A); illustration of the immersive, first-person perspective (B); three snapshots from the graphics design process (C).

Our goal was to design a multipurpose VR environment compatible with standard computer specifications, so that it can be used easily in almost any laboratory. To our knowledge, this is the first open-source, publicly available VR environment that provides two modes of interface, easily capturing a wide range of scenarios, while also enabling experienced developers to add new features and customize the environment to their experimental/clinical needs. We present the successful pilot testing of two completely different applications, in different laboratories, for different physiological modes of interaction, using different interfaces (i.e. accelerometers vs rt-fMRI), as evidence of the versatility and multi-purposefulness of this VR environment. The two test applications can be used without necessarily modifying any settings, as long as the input from the hardware in test application 1 and of the real-time analysis in test application 2, meets the respective engineering and computational descriptions we provide explicitly in the Methods.

III. METHODS

In this section we present the overall considerations and motivation for the design of the 3D computer graphics and the data management options for the multipurpose VR environment. Subsequently, we present the apparatus, procedure and computations associated to each of the first two test applications. The VR task only encompasses running, however it provides both direct performance feedback (via the visualization of the user's bodily movements in real-time for the motor rehabilitation application and via the speed of running in the neurofeedback application), as well as secondary feedback and performance metrics, via the information illustrated in Fig. 1-4. Secondary tasks were not relevant in the context of our pilot applications but can easily be incorporated by experienced or intermediate Unity programmers, to fit the purposes of other studies or clinical contexts. The difficulty level in both apps can be readily adjusted, directly in the code, via the calibration of the hardware or via variations in real-time data analysis procedures.

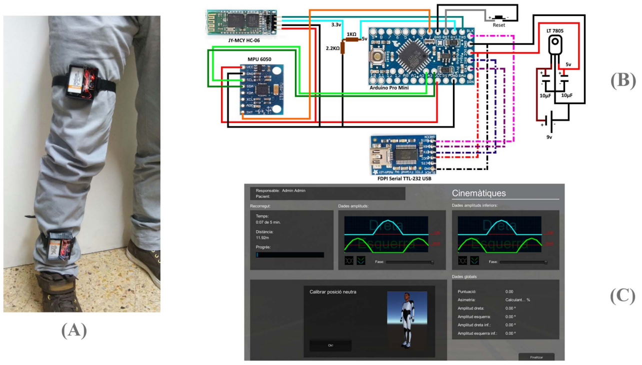

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Fig. 2. Application to motor rehabilitation. Device mounting (A); hardware connection scheme (B); real-time data (C).

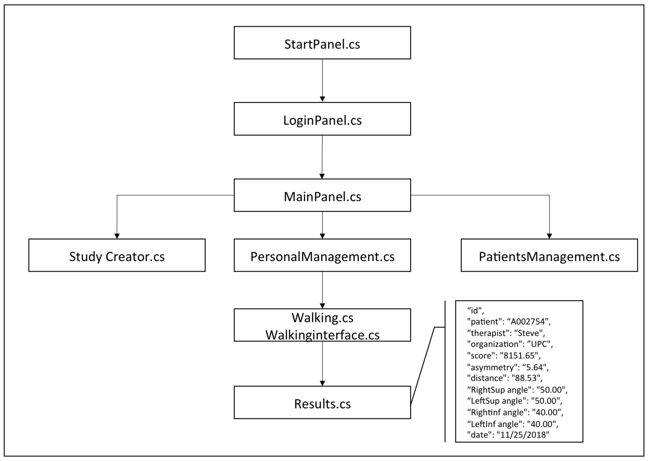

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Fig. 3. Workflow diagram detailing the C# software components of the motor rehabilitation application.

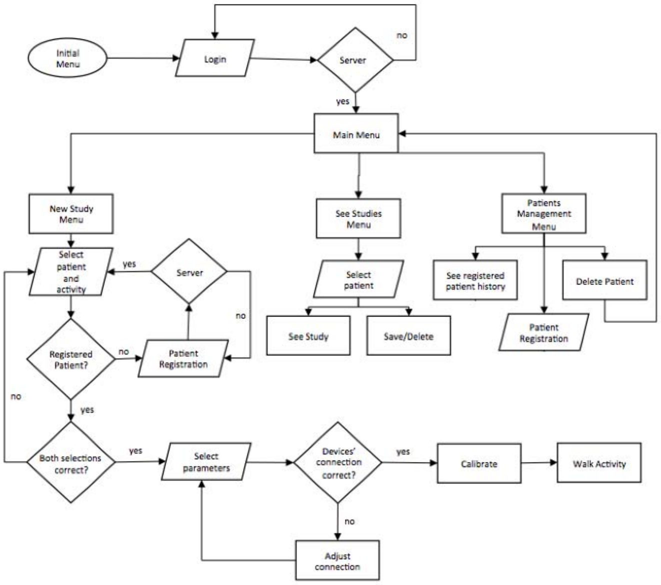

Fig. 4. Functional architecture of motor rehabilitation application. Diamonds represent decision points, rectangles represent system processes and parallelograms represent menu options.

In the two presented applications, the motivation of the participants relied on the wish to improve their motor function or on excitement regarding the possibility of controlling a video-game with their mind. In this sense, the environment itself was only the background medium used to convey information about the user’s own body/brain function.

The multipurpose VR environment was created using Unity 5.5.1f1 [35] and was recently updated to the latest LTS version (2017.4.18f1 - released January 2019). Unity is a game engine that is widely used for video game applications, compatible with many systems, from PCs and gaming consoles to mobile devices and websites. With Unity, it is possible to create 2D or 3D applications using object-oriented programming, via the C# programming language, where each object provides a specific functionality. The following procedure was used for the design of the computer graphics. Starting with a completely flat terrain, the first step was to give shape to the landscape. The relief was modified by adding textures, trees and grass through the use of specialized Unity built-in modeling tools. An avatar character was created using the third-party Autodesk Character Generator [36]. The avatar can be easily modified or replaced. The possibility of using the application in first-person view or third-person mode was enabled by the inclusion of several different virtual cameras (Fig.1a).

An application using the developed VR environment, can optionally include a graphical user interface (GUI) for data management. Via the data management GUI, data protection via username/password login can be enabled, a feature that was developed with applications related to confidential medical data in mind. Another optional feature, regards a server database application developed in Hypertext Preprocessor scripting language (PHP), that can collect information about the institution where the software is used as well as the performance statistics, facilitating multi-center collaborative research and/or clinical monitoring in multiple locations, via local or remote databases.

We provide our software in open-source form, to catalyze developments in this field by saving colleagues the time that would be required to recreate or replicate a virtual environment like this one. In doing so, we have considered several design principles that ensured this VR environment to be compatible with practically every existing neurophysiological modality. The applications we present here serve only as a proof of concept. Our goal is to inform the readership of our work and initiate a community of interested scientists and VR enthusiasts on GitHub, where researchers can submit issues and requests regarding the features that would be most meaningful to implement for specific studies and real-world clinical situations.

A. Test Application 1: Motor Rehabilitation for Lower Limbs

The aim of the first test application developed using the VR environment was to make the process of rehabilitation more enjoyable and effective, for patients who have suffered an injury or who have another mobility problem involving their leg(s). It should be noted that this application was developed for subjects with motor deficits who can benefit from physiotherapy and specifically gait training. Subjects can be immersed in the VR environment from a first-person visual perspective, so that they have the sensation that the virtual legs are their own. Using four accelerometers placed on a subject's physical legs, the application can detect movement and apply it to the virtual legs, resulting in movement within the VR environment. Virtual movement changes according to user speed and angular positions, and clinicians can modify the settings according to each patient's mobility performance.

The test application works using four accelerometers connected via bluetooth and controlled by an Arduino board. SteamVR (version 1.2.7) facilitated exporting the project, while ensuring compatibility with multiple devices. During design, we tested using both Oculus (firmware version 2.10) and HTC Vive (ViveDriver version 1.1.0.8). The simplest way to make the app compatible with older headsets, is to re-export it from Unity, according to specific, older or alternative project formats.

During the software development, Oculus Rift DK2 VR glasses were used, featuring a resolution of 2160 × 1200 pixels and a vision angle of 110° [37]. Additionally, an Intel Core i7 6th generation computer workstation with 8GB RAM, 1TB storage, and a NVIDIA GeForce GTX 970 high performance graphics card was used. The developed software source code can be easily adapted for usage with other devices. The minimum computer requirements comprise of an Intel i5 5th generation processor, 8GB of RAM and a NVIDIA GeForce GTX 960 or similar high performance graphics card. Moreover, the required apparatus must incorporate an accelerometer and a gyroscope that can read data in three reference axes, similarly to the detailed connection scheme displayed in Fig. 2. A calibration of the accelerometers is necessary for each patient during the initiation of a session. During the software development, using the Arduino Pro Mini ATmega 328P was preferred due to its compact dimensions of 18 × 33 mm. This model operates at 5V and 16 MHz. For the purposes of the laboratory setup, pins were welded in-house on a custom board with 14 pins of input/output, 6 analog inputs and additional space for mounting other connectors. The hardware configuration consisted of four Inertial Measurement Unit (IMU) devices. IMUs are electronic devices that measure and report the speed, orientation and gravitational forces of a device, using an accelerometer and a gyroscope. Specifically, the MPU-6050 model (Invensense Inc.), used during development, has six degrees of freedom. It combines a three-axis accelerometer and a three-axis gyroscope and operates at a sampling frequency of 100 Hz using 3.3V. The bluetooth module JY-MCU HC-06, that is fully compatible with the Arduino, was selected due to its compact size that deemed it ideal for the project. Finally, a FDPI USB-to-TTL serial cable, with an embedded FTDI FT232RL USB-serial chip, featuring a six-pin socket with 5V power and ground, as well as RX, TX, RTS and CTS connectors at 3V logic levels, completed the VR lab setup for motor rehabilitation (Fig. 2).

A VR installation featuring the described setup, was installed for two weeks in the neuro-rehabilitation hospital premises of the Guttmann Institute in Barcelona, following approval by the institution's internal committee. No data were exported from the hospital. Five physiotherapists participated in the pilot trials, aiming primarily at usability testing. The physiotherapists were given free access to the installation and were encouraged to incorporate it in physiotherapy sessions with their personal patients. Each clinician tested the application with at least one suitable patient, at least once.

During a VR motor rehabilitation session, a patient can be immersed in the landscape in the form of an avatar, in first-person perspective, so that the patient has the sensation that the virtual legs are his/her own (Fig 1). Using four accelerometers placed on the patient's legs (Fig. 2), the application can detect movement and map the movement to the VR environment. Depending on the magnitude of the movement of the patient's leg, that can vary anywhere between a twitch and a complete step, each leg movement is mapped into a complete step in the VR environment. In each session, the exact magnitude threshold that can trigger a complete step in the VR environment, depends on the preceding calibration, the current abilities and rehabilitation stage of each participant. This way, even patients with limited mobility can have the rewarding and encouraging experience of walking and jogging in a virtual environment. During the performed tests, each round of practice lasted a maximum of five minutes.

The data from a session using the VR environment for rehabilitation following leg injury are updated in real-time, as well as stored and summarized on a screen at the end of each session. The information displayed includes: a) The patient name or code and the name of the researcher or clinician; b) Real-time updates of the distance travelled, the time taken, and the remaining length of the session; c) Real-time information on the current amplitudes of the superior (above the knee) and inferior (below the knee) angle of flexion of each leg; d) Real-time information on the average amplitudes of the superior and inferior angle of flexion of each leg, since the beginning of the session; e) Real-time information on the asymmetry α, in accordance with (1) and (2).

$$\theta(t) = \theta(t-1) + \sum_{n=t-w-1}^{t-1} \Delta\theta(n) \tag{1}$$

$$\alpha = max\left\{\frac{\theta_{SR}+\theta_{IR}}{\theta_{SL}+\theta_{IL}}, \frac{\theta_{SL}+\theta_{IL}}{\theta_{SR}+\theta_{IR}}\right\} \tag{2}$$

where $\theta(t)$ represents the angular position in a measurement location at time t, $\Delta\theta$ represents the change in angular position between successive sampling points, w represents the angular position update window and SR, IR, SL, IL represent the measurement locations Superior-Right, Inferior-Right, Superior-Left and Inferior-Left, respectively. For the purposes of the application, w was set to 10 samples; that is the angular velocity was updated every one second.

The application is calibrated at the beginning of each session. The patient performs minimum and maximum flexion, therefore, more or less speed is assigned in the virtual path depending on the range obtained in the calibration. In this way, the patient can be encouraged to achieve maximum speed and maintain it.

Fig. 3 illustrates the main software components running in the background during the application for motor rehabilitation. A script called LoginPanel.cs loads the graphical user interface for entering login credentials. PrincipalPanel.cs enables the user to select one out of three possible tabs. During a session, Walking.cs and WalkingInterface.cs run simultaneously, collecting and processing Arduino data. Once the study is finished, the results are visualized on the screen via Results.cs. The results can additionally be sent to external modules for further processing or storing. Fig. 4 illustrates the possible interactions between menu options, system processes and decision points.

B. Test Application 2: Real-Time Functional Neurofeedback

Motivated by recent reports of successful self-regulation of brain activity using VR environments, particularly with electroencephalography [33] and functional near-infrared spectroscopy [34], we developed a VR rt-fMRI neurofeedback paradigm at the Barcelona β eta Brain Research Center, in Barcelona. Five volunteers participated in pilot testing, following approval by the local ethics committee "CEIC-Parc de Salut Mar" that reviewed and approved the experimental protocol. The speed of movement in the VR environment was modulated by the efficiency of self-regulation of brain activity. The specified brain region of interest (ROI) was the CA1 subfield of the hippocampus, an area that is expected to show changes in brain function during the early, asymptomatic stage of Alzheimer's disease [38].

A Philips Ingenia CX MRI scanner, operating at 3 Tesla, was used, featuring Philips console software version 5.1 and the Philips external control (XTC) patch. Apart from the Philips image reconstruction and MRI console PCs, two additional computers (Intel i7 6^{th} generation processors, 16GB RAM), running Windows 7 Enterprise edition and in-house neuroimaging analysis software with dependencies on Matlab 2013b (Mathworks Inc.) and the SPM12 toolbox [39], were additionally used. The PCs were connected as illustrated in Fig. 6. Apart from the image reconstruction PC, the rest of the computers were connected via shared folders through the local area network (LAN) and file transfer was facilitated through MS-DOS batch programs and the Philips "Corba Data Dumper" application. The digital audio-visual stimulation system VisuaStimDigital (Resonance Technology Inc.), featuring MRI-compatible goggles with fiber-optic communication, were used to present the VR environment to the eyes of a volunteer undergoing functional MRI scanning.

Scanning using a 32-channel headcoil. Prior to the rt-fMRI measurements, a high-resolution (1×1×1 mm) T1-weighted anatomical reference image was acquired using a rapid acquisition gradient echo sequence. Echo planar imaging was used with an echo time of 35 ms and a repetition time (TR) of 3 s. Slice-acquisition was interleaved within the TR interval. The matrix acquired was 80×80 voxels with a field of view of 240 mm, resulting in an in-plane resolution of 3 mm. Slice thickness was 3 mm with an interslice gap of 0.2 mm (45 slices, whole brain coverage).

Each EPI image of whole-brain activity was acquired, reconstructed and exported with minimal delay, every three seconds, via the local area network (LAN), to the real-time analysis computer (Fig. 6). Each volume was analyzed in approximately 800 ms. We estimated that the average time required to write the text file to disk was in the order of 250 ms. Thereby the visual signals were updated approximately every 3 s with a lag of approximately 1s from each volume acquisition.

Movement correction through rigid-body registration to an initial reference volume, temporal high-pass filtering with a cutoff frequency of 1/200 Hz to remove low frequency drifts in the rt-fMRI time series [40], and voxel efficiency weighting [41] through voxel-wise normalization within a sliding time-window, were applied in real-time to the online data. Voxel-efficiency weighting was performed by normalizing new images based on the mean and standard deviation of the preceding observations in each voxel, according to (3).

$$z_t = \frac{X_t - \bar{X}_{(t-w-1)..(t-1)}}{\sigma_{(t-w-1)..(t-1)}} \tag{3}$$

where, at time t, z_t represents the efficiency-weighted value in a single voxel, X_t represents the unweighted value of that voxel, $\bar{X}_{(t-w-1)..(t-1)}$ represents the mean and $\sigma_{(t-w-1)..(t-1)}$ represents the standard deviation of the timeseries within a specified time-window, of length w, up to time $(t-1)$. For the purposes of our testing, w was set to 30 scanning volumes.

An outcome variable was instantiated for the activity measured within a region of interest (ROI), for each acquired brain volume, according to the following computations. The expected data vector $\mathbf{Y}$ at time t_0 was computed as in (4).

$$\mathbf{Y}(\mathrm{t}_0) = \sum\nolimits_{t=(t_0-w-1)}^{t_0-1} \frac{\mathbf{Z}(t)}{w} \tag{4}$$

where $\mathbf{Z}$ (t) represents the voxel-efficiency-weighted observed data vector from the ROI at time t and w represents the length of the specified sliding time-window (30 volumes). For each new volume acquired in real-time, a non-linear metric *NF* was computed according to (5).

$$NF = \bar{\mathbf{Z}}(\mathrm{t}_0) - \bar{\mathbf{Y}}(\mathrm{t}_0) \tag{5}$$

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When the average expected signal in the ROI surpassed the average observed signal of the ROI in the new volume, the velocity v in the VR environment was increased by 5% as in (5); in the opposite case, the velocity was decreased by 5% as in (6).

$$NF < 0 \rightarrow \Delta v = 0.05 \tag{6}$$

$$NF > 0 \rightarrow \Delta v = -0.05 \tag{7}$$

where v represents the velocity of movement in the VR environment.

This procedure resulted in a closed-loop, non-linear, adaptive, sliding window paradigm, enabling continuous neurofeedback throughout the scanning session. The first 10 scanning volumes were discarded to allow for magnetic field saturation. The initial baseline ROI mean and standard deviation were computed based on the following 30 functional volumes, during which the VR velocity was maintained at 50%. After the initial reference baseline was established, every three seconds, the real-time neuroimaging analysis variable was communicated to the VR presentation PC, resulting in a modulation of the velocity of movement in the VR environment (Fig. 6). The velocity of movement was increased by 5% when changes in the neural activity within the ROI were in the desired direction or decreased by 5% when changes in the neural activity within the ROI were in the opposite direction. The velocity would remain stable in the highly improbable case of no change in neural activity.

Interfacing between Matlab and Unity was enabled by using a simple text file employing a standard data format convention. The first line of the file featured one number in the $\{-1{,}0{,}1\}$ range, representing whether the outcome of the real-time neuroimaging analysis implied that the VR velocity should be decreased, remain stable, or be increased respectively. The neurofeedback signal text file was modified once for every acquired functional volume. The second line of the file featured one value that alternated between 0 and 1 each time that the file was modified. In Unity, a timer object checked whether the second line of the file had been modified, every 5 ms. Whenever the file had been modified, Unity would read the value from the first line and modify the VR velocity accordingly. That is, the Unity timer object (5 ms) relates to how often Unity checks to see whether Matlab has updated the output file of the real-time neurofeedback analysis.

This system easily enables to replace the rt-fMRI analysis with any other real-time analysis that can produce an output in the same format, via Matlab or any other data processing software. The approach was validated during the development phase, using computer scripts that generated simulated data, serving as the instructions for VR control.

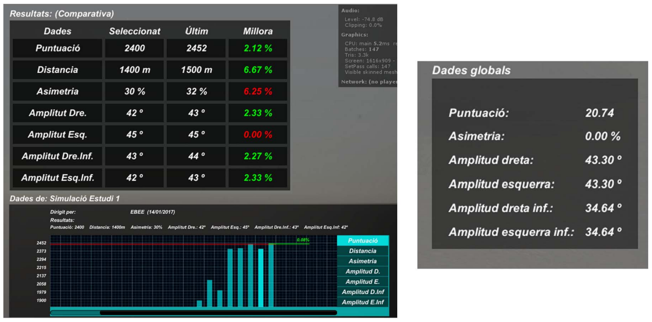
IV. RESULTS

In this section, we present the results and information relating to the pilot testing of each of the first two test applications that have used the multipurpose VR environment.

A. Test Application 1: Motor Rehabilitation for Lower Limbs

The resulted motor rehabilitation application features both visual and auditory components: the virtual speed that depends on the physical movement, as well as the sound of footsteps that is also synchronized with leg movements. The sound of the footsteps depends on the ground that the avatar is stepping on (e.g. dirt road vs wooden bridge). That makes the experience more immersive and realistic. The application also features an auditory soundscape that simply complements the visual environment with calming park sounds (birds, water waves, etc.).

Via semi-structured interviews, physiotherapists reported unanimously positive responses to the application. Further user tests will be conducted in the future. Historical data captured in the application, include the date, score, asymmetry, time, distance and left and right angles of flexion. During the sessions, clinicians can also evaluate performance based on the generated graphs (Fig. 1-2). The patients themselves also offered positive feedback overall. They enjoyed the use of the application and reported that it facilitated their rehabilitation exercises, by making them more enjoyable. The patients emphasized that the immersiveness of the experience was a key factor, in enhancing their training.



Resultats: (Comparativa)

Dades	Seleccionat	Últim	Millora
Puntuació	2400	2452	2.12 %
Distancia	1400 m	1500 m	6.67 %
Asimetria	30 %	32 %	6.25 %
Amplitut Dre.	42 °	43 °	2.33 %
Amplitut Esq.	45 °	45 °	0.00 %
Amplitut Dre.Inf.	43 °	44 °	2.27 %
Amplitut Esq.Inf.	42 °	43 °	2.33 %

Audio:
Level: -74.8 dB
Clipping: 0.0%
Graphics:
CPU: main 5.2ms
Batches: 147
Tris: 3.3k
Screen: 1616x909 -
SetPass calls: 147
Visible skinned mesh
Network: (no player

Dades de: Simulació Estudi 1

Dirigit per: EBEE (14/01/2017)
Resultats:
Puntuació: 2400 Distancia: 1400m Asimetria: 30% Amplitut Dre.: 42° Amplitut Esq.: 45° Amplitut Dre.Inf.: 43° Amplitut Esq.Inf: 42°

Dades globals

Puntuació: 20.74
Asimetria: 0.00 %
Amplitud dreta: 43.30 °
Amplitud esquerra: 43.30 °
Amplitud dreta inf.: 34.64 °
Amplitud esquerra inf.: 34.64 °

(A) (B)

Fig. 5. Exemplary results from a VR-facilitated motor rehabilitation session (A); global data computed (B).

During a VR motor rehabilitation session, real-time results are displayed in a screen that is only visible by the investigator or clinician, because the patient is immersed in the VR environment, viewing through the VR goggles. After the end of the VR session, the final results summarize the performance data and overall progress, in relation to previous sessions. Selecting a particular metric (e.g. “Puntuacio”, i.e. Score; Fig.5) displays the history of performance on that metric across sessions. This setup allows to easily monitor progress and to intuitively identify the exact sources of improvement, as well as the muscles that require more exercise.

In this pilot application, the goal of the participant is to walk in place; that is, without moving in the real-world, physical space. This was so because the test application was designed for patients with limited mobility. An additional merit of this approach is that it allows for the usage of the application even in rooms with limited space. Each step is executed in an “all or nothing” fashion. That is, if the movement surpasses a certain magnitude, a complete step is triggered. The threshold of the movement magnitude that can trigger a step is determined at the beginning of a session, during the process of calibration. During the calibration process, the patient performs minimum and maximum flexion of the knee. The speed that is assigned in the virtual path depends on the range obtained during calibration. A patient with very low mobility will have to perform smaller movements than a patient with more mobility, to achieve the same speed. However, all patients will be able to move at maximum speed if they perform the maximum movement that is within their comfortable movement range. In this way, all patients are encouraged to exercise the full flexion that they can attain without risking any injury due to overzealous effort and strain. The VR environment serves to make this type of physiotherapeutic exercises that are normally extremely monotonous, a bit more exciting. In this context, the IMU measures the speed, orientation and gravitational force, using accelerometers and gyroscopes. We use the accelerometer values, to calculate angles and angular positions. During a training session, the change of angle determines the speed of each step.

During our pilot tests, motor rehabilitation sessions using the application were limited to a maximum of five minutes.

That does not prevent running many sessions in a brief period of time (e.g. six sessions within one hour). However, this should be done under the supervision of a qualified clinical physiotherapist. Varying the difficulty of the task during a session is possible by adding a simple line to the code of the real-time processing file, that increases the threshold of movement magnitude required for a step to be triggered. However, that was not desirable for our pilot tests, especially because they were conducted under the supervision of a clinical physiotherapist who retained full control of the session and had the ability to provide individualized verbal feedback and instructions, to guide the patient into optimizing performance without risking any damage to the recovering nerves and muscles. As mentioned, the difficulty of the task is calibrated at the beginning of each session, which offers a way to gradually increase the difficulty without risking that the level of difficulty and immersiveness may cause any harm to the patient.

In the developed application, clinicians/researchers are in the position to specify a code for each participant, so the compliance with local policies on data protection are in the hands of the clinicians/researchers and depend on the quality of the anonymization procedures they utilize. The application simply provides the features to enable them to manage effectively situations where other lab users may have access to the same computer with similar permissions. In such a scenario, the usage of the application and the access to the information of specific patients can be protected via the username and password of the clinician responsible for each patient. This way, each clinician can access the data of their own patients only and not those of any other patients. A new study can be created for new patients or a new session for returning patients. Stored data from previous visits are easily accessible via a specialized "Studies" tab. A "patient management" tab can be used to add new patients and to access a patient's performance history.

B. Test Application 2: Real-Time Functional Neurofeedback

The described real-time processing approach results in adaptive task difficulty, due to using a sliding-window as the adaptive baseline reference activation. In the case of good performers, the algorithm pressures them to perform even better. In the case of bad performers, the algorithm makes performance easier until it meets a comfortable level for the participant and then it pressures them towards improving. This is reflected in Fig. 6b, in the context of hippocampal down-regulation. The figure shows that the participant down-regulated hippocampal activity effectively to what appears to be the plateau of minimum activation possible.

The neurofeedback application provides mostly visual feedback for the time being. The visual feedback offered by the neurofeedback application consist of a green signal when brain activity changes in the desired direction, or a red signal if brain activity changes occur in the opposite direction. The speed of movement also depends on these changes. The aim was for participants to learn to control their brain, specifically to down-regulate the activity of the hippocampus. This may lead to a clinical application in the future because hippocampal hyperactivity is a sign of Alzheimer's disease [42]. The inherently pleasant sensory experience of acceleration acts as an implicit reinforcer of the behavior that we require the subject to learn, repeat and master, while the deceleration acts as a negative reinforcer, making the unwanted behavior less likely to occur in following trials.

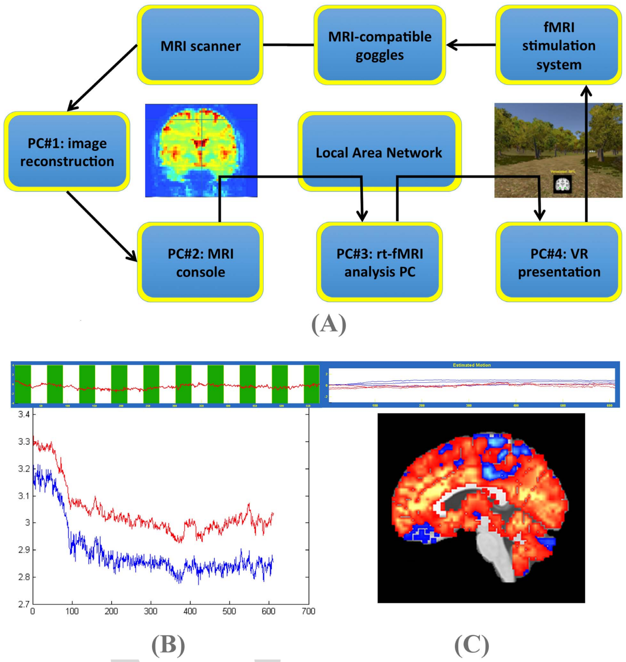


Fig. 6. Application to real-time neuroimaging. In the rt-fMRI neurofeedback setup, the computers handling data reconstruction, data storage, data processing and presentation of the VR environment are interconnected serially or via the local area network (A). The real-time information available to investigators includes non-linear ROI signal change (top-left), motion parameters (top-right), ROI mean and median (bottom-left) (B). An innovative feature of the implemented paradigm is that it enables to investigate the whole-brain functional connectivity of the region of interest during or after the VR neurofeedback self-regulation of neural activity (C).

Researchers are given the option of activating the sound of the footsteps and the rest of the soundscape, similarly to the motor rehabilitation application. However, subtle sounds are often masked during fMRI due to scanner noise [43]. Moreover, the auditory changes (e.g. sound of steps on a dirt road vs on a wooden bridge) would likely introduce structured patterns of activity variation in the auditory cortex and associated brain regions, which is undesirable in real-time functional neuroimaging.

Similarly to the motor rehabilitation test application, all volunteer participants reported positive feedback overall, with regards to their experience using the application continuously for 30 minutes. During a VR real-time neurofeedback session, real-time results are displayed in a screen that is only visible by the investigator or clinician, because the subject is immersed in the VR environment, viewing through the VR goggles. Available real-time data include the three translation movement parameters in mm (X, Y, Z), the three rotation parameters in degrees (pitch, roll, yaw) and the non-linear

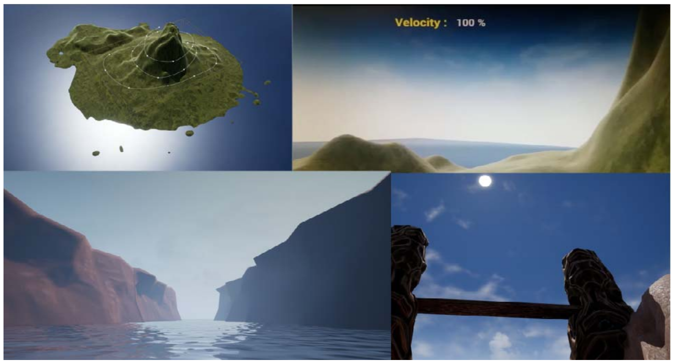


Fig. 7. Future directions. Graphical snapshots from the upcoming, second generation multipurpose VR environment, featuring additional activities (i.e. swimming and flying), designed to enable versatile training within a single session.

metric *NF* that determines neurofeedback updates (Fig. 6), computed as in (5).

At the end of the session, a VR score is immediately accessible, summarizing the distance travelled in the VR environment, which reflects neurofeedback performance. The neuroimaging data are also available for offline analyses to investigate the average activity within the ROI or the functional connectivity of the ROI with the rest of the brain (Fig. 6). Additionally, a logfile is generated at the end of each session, documenting the sequential velocity values experienced by the subject. As with the motor rehabilitation application, the researcher has the option to give the logfile any name, that usually corresponds to the participant's anonymized code.

V. Discussion

AQ:3 We have created a multipurpose VR environment that has been used in two very different test applications, representative of two much wider general categories of applications. The motor rehabilitation test application can be easily used in any study or clinical context where the movement is meant to be controlled by two actuators; these can be linked to limb movements as easily as they can be linked to e.g. eye movements. Using the same environment with e.g. electromyographic actuators, would simply require modifying one computer code file that implements the real-time data analysis. Similarly, the neurofeedback application can be easily used in any study or clinical context where the moment-to-moment changes of interest can be summarized by a single value; that is, studies where a single, one-dimensional variable can be extracted in a continuous manner. In both applications the design is completely modularized so that the output of any real-time analysis (e.g. from electroencephalography to thermometry) can interface with the VR environment. To our knowledge, this is the most up-to-date open-source, adaptive, multipurpose VR environment that can be used for several, different biomedical and health applications. The framework developed, provides features of clinical relevance, such as password protection options for data confidentiality, history logging and session management tools, automated performance tracking and real-time monitoring.

Due to the capacity VR offers for sensory immersion, the presented VR environment can be used for neurofeedback training as well as to facilitate rehabilitation following leg injury. In both cases, the user's activity controls virtual movement. In the case of rehabilitation, the calibrated displacement of the patient is reflected through a virtual avatar with synchronous movement. Virtual steps are typically of greater magnitude than the triggering physical movements, thereby encouraging progress in recovery. In the case of rt-fMRI neurofeedback, changes in brain function processed in real-time, control the speed of movement in the VR environment, reinforcing learning of self-regulation with regards to the activity within a pre-specified brain area.

It is noteworthy that providing a VR environment that can be readily used especially for motor rehabilitation is very important because a recent review suggests that VR interventions are at least as effective as conventional physiotherapy in improving lower limb outcomes in stroke patients [19]. Such VR interventions have focused on training balance [], postural control and gait control, [26], [28], [44]. Effects have been shown to be stronger with regards to functional balance, gait velocity, cadence and stride length. This is the reason why in the motor rehabilitation test application, we focused on parameters relating to similar concepts. In the neurofeedback test application, the environment is compatible with the use of any brain region or network as the neurofeedback target. Overall, in our approach, the biological point of interface with the VR environment can be selectively specified in accordance with the focus of a scientific investigation or clinical application.

Immersiveness is an important factor that must be taken into consideration when developing a multipurpose VR environment. Immersiveness is important in encouraging effortless engaging in VR training and therefore leads to higher effectiveness and better therapeutic outcomes [44]. In the presented motor rehabilitation test application, we achieved a high level of immersion by incorporating a detailed mapping of the environment using both primary senses (i.e. vision and hearing). The participants were able to see their movement in the VR environment as well as to listen to their steps and the soundscape of the designed environment that featured birds, waves etc. Similarly, in the neurofeedback application, we utilized the perception of acceleration and mechanisms of sensory-aided learning, to exert effects of operant conditioning via implicit reinforcement.

Adaptability is of utmost importance in providing a smooth learning curve to the user. Previous work has emphasized the utility of VR due to it's capacity for manifesting adaptive task difficulty [45]. In principle, task difficulty can be constantly, programmatically adapted to the user's performance. In the presented motor rehabilitation application that is accomplished per session, based on session-specific calibrations. This is the secondary reason for recommending five-minute-long sessions, apart from ensuring that the user is not subjected to excessive physical stress. The scaled real-time reflection of patient movement in the avatar's steps is a characteristic that allows for a highly personalized experience and can help to improve the therapeutic utility of the system, by providing graded and individualized rehabilitation activities [46]. In the presented neurofeedback application, the task difficulty is adapted by means of the described data analysis procedure. Because successful performance on any given three-second trial is dependent on the performance during the preceding 90 seconds, the task becomes increasingly difficult for good performers. Similarly, the task becomes progressively easier for bad performers. The latter are therefore given the opportunity to start from a comfortable level and increase their activation level incrementally. The overall aim is to drive all users to their optimal performance.

It is our recommendation that for many biomedical applications, the task must not be too distracting for the patient, so that the environment only serves as a medium that facilitates directing focused attention to a part of the physical body, rather than to entertaining but distracting, complex artificial features. We also recommend maintaining perceptual and cognitive load steady across a session, so that arbitrary effects, e.g. in brain activity, are not introduced by the sudden appearance of unanticipated stimuli. Due to such considerations we decided for the implementation to be realistic enough to guarantee an immersive experience, yet relatively minimalistic, to avoid distractions and inhomogeneous experiences.

In conclusion, we attribute the effectiveness of our approach to a noteworthy combination of three principles implicit in the design. First, selectivity, referring to the flexibility to focus the responsiveness of the VR environment to any particular metric, behavior or physiological modality of interest. Second, immersiveness, which functions as an engaging, motivating factor that prolongs the duration of the exercises and hence the probability of an effective therapeutic outcome. Third, adaptability of the VR environment and task to the level and capacity of each patient. The latter is equally important in ensuring long-term engagement and therapeutic progress.

Due to the open-source provision of the software and its modular design, the VR environment offers extensibility to richer virtual features as well as to different modalities, making it highly suitable for use in multiple different scenarios. It is very easy for experienced or intermediate Unity programmers to add new features to the environment. Such features can be designed from the bottom up or even be bought online and placed within the environment. The integration of new features is seamless and these features can vary widely from an additional tree, to a house, to an interactive character.

A minor limitation of the current version of the VR environment, is that it can become repetitive when used for extensive time periods. A variety of virtual landscapes and virtual objects are currently being designed to alleviate this identified shortcoming and to ensure a more fun and memorable experience, even during long sessions. The forthcoming, second edition of the presented VR environment, aims to encompass further innovative features, such as simultaneous representation of activity from multiple sources (e.g. upper and lower limbs or two independent brain regions). This future version of the VR environment will feature auditory feedback, that goes beyond complementing the visual environment for increased immersiveness. In the future version, auditory feedback will also be usable to convey changes in a variable of interest, e.g. brain activity or task difficulty. We are also aiming to make the application more interesting, so that it can maintain the user's interest for longer time intervals. At the same time, we are maintaining the application backwards compatible. The task variations we will add to running, are swimming and flying. This allows for more flexibility with regards to experimental designs; e.g. by separating the session into different tasks and using one brain area for running and another brain area for swimming. This also enables the inclusion of randomized placebo trials and other features that will be of great interest to the scientific community. An untested alpha version of the future version is currently under development on GitHub and we anticipate the final version to become publicly available in early 2020.

In the context of motor rehabilitation, an application for rehabilitation following injury of the upper limbs is currently under development. This application will be available for different operating systems such as Android, iOS and Windows. Making the application accessible on common devices will enable a cost-effective solution that can be easily adopted in a wide range of settings.

In the context of the rt-fMRI neurofeedback application, the use of a TCP/IP server is also being explored. Such an option will enable the VR application to interface with the real-time analysis pipeline more robustly. Further VR features, scenarios, objects and characters will be introduced in the future, allowing, among other options, to assess the activity in different ROIs within the same scanning session. In the long run, the aim is to design experiments with complex cognitive tasks and with modulating cognitive demands that may facilitate the estimation of measures of neural capacity and efficiency in specific ROIs.

We envisage the development of a variety of other applications, using the developed multipurpose VR environment, potentially using additional devices to capture physiological changes, from electrodes for electromyography to webcams for emotion-related facial temperature changes. The VR environment is available as open-source software, under a Creative Commons license, via a GitHub repository [47].

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