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Modulating verticality representation and uprightness by virtual reality: rationale and protocol for a within-person randomised intervention associating a basic study in healthy individuals and a pilot clinical trial in individuals exhibiting post-stroke lateropulsion (VIRGIL)

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ABSTRACT

Introduction Balance and gait disorders represent the most frequent and disabling sequelae after stroke. Impaired body orientation with respect to gravity (lateropulsion) is one of the primary underlying mechanisms, increasingly investigated. After hemisphere stroke, lateropulsion is caused by an impaired internal representation of verticality, for which developing rehabilitation techniques has become a priority. Among various approaches, virtual reality appears to be a promising tool for modulating spatial reference frame. The objective of this study is to investigate the effects of immersion in virtual tilted reality (VTR) on the postural vertical (PV) as a primary outcome, as well as main secondary outcomes on the visual vertical (VV) and the active standing posture (body orientation with respect to gravity and weight-bearing (WB) distribution on lower limbs), both in healthy individuals and individuals exhibiting lateropulsion at the subacute phase after a hemispheric stroke. The cumulative effect of the VTR on the post-stroke lateropulsion will also be analysed.

Methods and analysis This pilot study is a single-centre, within-person randomised trial conducted in the department of Physical and Rehabilitation Medicine of the University Hospital of Grenoble-Alpes (France). We will include 40 individuals from 18 to 85 years old, 20 healthy individuals and 20 individuals with lateropulsion tested <9 months after a hemisphere stroke. Both groups will be matched on age. Each VTR immersion lasts about 45 min. For healthy participants, the study duration is two half-days, one devoted to testing the effect of VTR on verticality perception (PV and VV), and the other to test the effect of VTR on the active standing (body orientation with respect to gravity and WB distribution on lower limbs). For participants with post-stroke lateropulsion (score >0.5 on the Scale for Contraversive Pushing), the study lasts 4 weeks: W1 for inclusion, randomisation, planning and conventional rehabilitation; W2 and W4 to collect clinical data and conventional rehabilitation; and W3 for the VTR intervention over four consecutive mornings at the same time: 2 to test the VTR effects on verticality perception (PV and VV) and 2 to test the VTR effects on active standing (body orientation and WB distribution on lower limbs). Immediate effects and post-effects of the VTR immersion are analysed by comparing results of the following time points: for verticality perception baseline, during and after VTR and for active standing at only baseline and during VTR immersion. Linear mixed-effect models will be run with different factors/covariates according to objectives. We will analyse the proportion and features of responders (PV modulation ≥2°). The cumulative effect of the 4 days of VTR sessions will be analysed by comparing scores of the SCAle for LAteropulsion assessed at the end of every week.

Ethics and dissemination The study was approved by an institutional review board at the national level (Comité de

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The study design is a within-person randomised intervention.
⇒ The study associates a basic study in healthy individuals and a pilot trial of individuals exhibiting post-stroke lateropulsion.
⇒ The novelty relies on the intervention, based on immersion in virtual tilted reality (VTR), and on outcomes.
⇒ We analyse VTR effects on verticality perception (postural and visual vertical) and uprightness in standing (instrumental measurements of body orientation and weight-bearing asymmetry).
⇒ This is a pilot study with an exploratory design and limited sample size.

Protection des Personnes Ile de France X; 2020-A02941-38, amendment 2024). All participants will provide written informed consent before enrolment. Findings will be submitted to peer-reviewed journals related to rehabilitation, stroke or neuroscience.

Trial registration number ClinicalTrials.gov, NCT04911738.

INTRODUCTION

Background

Lateropulsion is a deficit of body orientation with respect to gravity,[1–3] which is frequent after stroke.[4] It increases the risk of falling[5] and is a primary cause of mobility limitation,[6–8] with poor recovery.[7–15] Lateropulsion comprises three postural signs in isolation or in association according to their severity:[3 16–18] a lateral body tilt, self-initiated lateral pushing and resistance to passive lateral tilting. The lateral body tilt is the cardinal sign, as shown by prevalence and principal component analyses[3] and stated by expert consensus.[17] After supratentorial stroke, lateropulsion is caused by an impaired internal representation of verticality (impaired sense of upright), tilted to the side opposite to the damaged hemisphere.[1 19]

Lateropulsion and its underlying mechanism, an impaired sense of upright after hemispheric stroke, represent major rehabilitation challenges because of their frequency and consequences on balance and gait disorders.[1 2 4] An effective approach should combine specific postural exercises[20 21] and a modulation of the internal model of verticality. Specific postural exercises are mainly based on tasks during which individuals are asked to actively orient their body with respect to gravity. Techniques that are supposed to modulate, even experimentally and transitorily, the internal model of verticality may be divided into three categories: (1) those modulating the gravity sensing,[22–28] (2) those directly stimulating the brain by magnetic or electrical techniques[29–32] and (3) those using visual clues tilting the environment in a given direction.[27 33–39] Evidence must be acquired for every technique, before incorporating those found relevant and efficient in rehabilitation programmes, which are crucially lacking so far.

Previous exploratory studies of healthy individuals[27] and case studies of individuals with stroke[40 41] suggest a clinical interest in immersing them in a tilted virtual environment to modulate their visual perception of the vertical or attenuate lateropulsion. We hypothesised that the effect could elicit a modulation of the internal model of verticality. This hypothesis implies that the effect is extended to several modalities of verticality perception: the visual vertical (VV), which is the only one tested so far, and the postural vertical (PV), never yet analysed for this purpose. It could also induce a change in the active body orientation with respect to gravity and weight-bearing (WB) distribution on lower limbs. Testing these hypotheses as well as the persistence of a post-effect is a prerequisite to incorporating the immersion in a tilted virtual environment in rehabilitation programmes dedicated to individuals exhibiting lateropulsion. Here, we present the protocol for the pilot study VIRGIL (VIrtual Reality Glasses use to Improve Lateropulsion through the post-stroke Postural Vertical) that addresses these questions.

Visual clues to modulate verticality perception: state of the art

Because lateropulsion is more severe without vision[42] and tilts in verticality estimates may be attenuated when visual clues are available,[33 34] the use of visual clues (eg, indices of verticality in the surrounding) is relevant for improving lateropulsion in individuals with a hemispheric stroke. Manipulating visual clues, static or dynamic, is also well known to have a powerful effect on verticality perception.[27 34 35 43 44] The seminal experiment of Wertheimer, in 1912, on the influence of a tilted visual frame on the verticality perception in healthy individuals was repeatedly replicated,[33 34] notably under the impetus of Asch and Witkin's pioneer work.[43] The work revealed a deviation of the VV towards the side of the frame tilt, now known as the 'rod-and-frame effect'. Notably, this perceptual frame effect was also found at the postural level,[36] with a strong influence of a static tilted environment on perception (verticality perception) and action (head and body lateral orientation) relative to gravity orientation, without interfering with postural stabilisation. Also, immersion in a real tilted environment[33 35 38] or a large-scale frame with a structural and meaningful three-dimensional enrichment[36 37] induced a stronger effect.

Thus, virtual reality seems a promising tool for implementing such immersion and manipulating the visual frame of reference. A recent pilot study[27] showed that briefly immersing (3 min repeated successively four times) healthy participants in a virtually tilted environment induced a powerful tilt (median 11.42°) of the VV toward the tilted side. Whether virtual tilted reality (VTR) might jointly affect the postural modality of verticality perception remains to be investigated. Such a transmodal influence would suggest not only a perceptual effect but also a modulation at the representation level. Moreover, the modulation effects reported in the previous study were transitory. A challenging question is whether longer and repetitive exposure to this VTR over several consecutive days might induce cumulative and lasting alleviation of the impaired verticality perception and recovery of lateropulsion. A recent single case study showed that even short presentations of tilted three-dimensional visual input could reduce symptoms of severe contraversive lateropulsion.[40] Such findings have sufficient clinical relevance to consider virtual reality as a potential rehabilitation tool. The tool may be able to recalibrate verticality perception in individuals exhibiting post-stroke lateropulsion due to an impaired internal model of verticality, thus alleviating their lateropulsion and improving their balance abilities.

Objectives and hypothesis

The VIRGIL study, a monocentric within-person randomised trial of healthy individuals or those exhibiting post-stroke lateropulsion, addresses four main novel questions: (1) Is the VTR effect on verticality perception transmodal? This implies that in addition to the modulation

of VV,[27] which mainly tests the vestibular contribution to gravity sensing,[45–47] VTR also induces a modulation of the PV, which corresponds to the perception of the vertical by the body and mainly tests the somaesthetic contribution of gravity sensing.[1 24 48–50] PV is more indicative than VV in lateropulsion.[1] This first hypothesis of a transmodality of the VTR effect is tested in healthy controls, in whom we predict that VV and PV modulations induce congruent tilts toward the side of the tilted environment. (2) Does this experimental effect improve VV and PV in individuals exhibiting lateropulsion in the subacute phase after a hemispheric stroke? To this end, stroke participants are immersed for 4 consecutive days in a virtual environment tilted to the side opposite to their contralesional lateropulsion. We predict an improvement in their verticality perceptions and lateropulsion. (3) Does the modulation of VV and PV persist over time after stopping the VTR immersion? And if so, how much time? This post-effect is a prerequisite for a possible clinical application. (4) Does this VTR-induced modulation of verticality perception extend to the active body orientation in standing? This situation would indicate the existence of a modulation bearing on perceptions, representation and action referred to verticality[51] and would pave the way for a clinical application of the VTR immersion for post-stroke lateropulsion rehabilitation. We predict a modulation of body orientation and bearing towards the side of the VTR. In addition, different instructions are given to participants for the standing condition; our hypothesis is that these instructions do not influence standing posture.

Finally, additional hypotheses are that most healthy participants and participants with a stroke will respond to the VTR (modulation of PV ≥2°), at least transiently. We will analyse the clinical profile of individuals with stroke responding to the VTR: the nature and severity of the deficits, localisation and size of stroke. We also hypothesise that participants are not aware of changes induced by VTR on the active body orientation in standing and that immersion in VTR does not induce discomfort.

METHODS AND ANALYSIS

The protocol was developed using the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) (additional material). The VIRGIL study is funded by the Fondation Paul Bennetot (France) and supported by the Virtualis company providing only the VTR device and programmes. The company had no role in the design of this study and its execution and will have no role in data analyses and interpretation or editorial decision to publish.

Design

This pilot study is a single-centre within-person randomised trial (ClinicalTrials.gov NCT04911738) conducted in the department of Physical and Rehabilitation Medicine of the University Hospital Grenoble-Alpes (France). Individuals with stroke are recruited among those admitted for rehabilitation after a hemispheric stroke. Healthy individuals are recruited via a public notice board. The study started in July 2021 and the end date is planned in March 2026.

Inclusion criteria

The inclusion criteria are, for all participants, (1) age 18–85 years, (2) social health insurance coverage and (3) giving signed, informed and free consent. Specific inclusion criteria for individuals with a stroke are (1) a right or left hemispheric stroke diagnosed by CT or MRI, existence of another brain lesion (hemispheric, brainstem or cerebellum) that enables inclusion; (2) time since stroke <9 months; (3) hospitalisation in the neurological physical and rehabilitation medicine unit; and (4) lateropulsion defined by a score >0.5 on the Scale for Contraversive Pushing (SCP).[52] This threshold used by our team has been found relevant many times to diagnose and analyse moderate and severe forms of lateropulsion.[1 3 4 6 16] Specific inclusion criteria for healthy participants are (1) no stroke or neurological disease history and (2) no previous disability interfering with balance, or vestibular disorders. The exclusion criteria for all participants are (1) darkness claustrophobia; (2) severe psychiatric disorders history; (3) advanced heart failure documented in the participant's medical records; (4) severe trunk deformation with C7 lateral deviation >30 mm due to any other disease apart from stroke (ie, scoliosis, leg length inequality, etc) or postural disorder history; (5) being in an exclusion period for another study; (6) under judicial or administrative supervision; (7) receiving more than €4500 compensation for participation in previous research involving humans in the 12 months before the study; (8) pregnant or breast feeding; and (9) under guardianship or a tutelage measure. Specific exclusion criteria for stroke participants are (1) unstable medical condition; (2) severe difficulty understanding, thereby preventing completion of assessments; (3) dizziness that compromises assessments; (4) neurological disorders interfering with balance; (5) untreated severe depression; and (6) inability to understand and execute simple orders. Subarachnoid haemorrhage is not a formal exclusion criterion if the individual's clinical picture corresponds to that of post-stroke hemiparesis.

Procedures

We use a standardised procedure with specific study duration for healthy individuals (figure 1) and individuals with stroke (figure 2). The effect of the VTR immersion is assessed with three tasks analysed in the frontal plane (PV, VV and active standing).

Healthy participants

For healthy participants, the study duration is two half-days (figure 3). After the inclusion visit and the signature of the informed consent, one half-day is devoted to the VTR effect on verticality perception (PV and VV) and the other to the VTR effect on standing posture (body

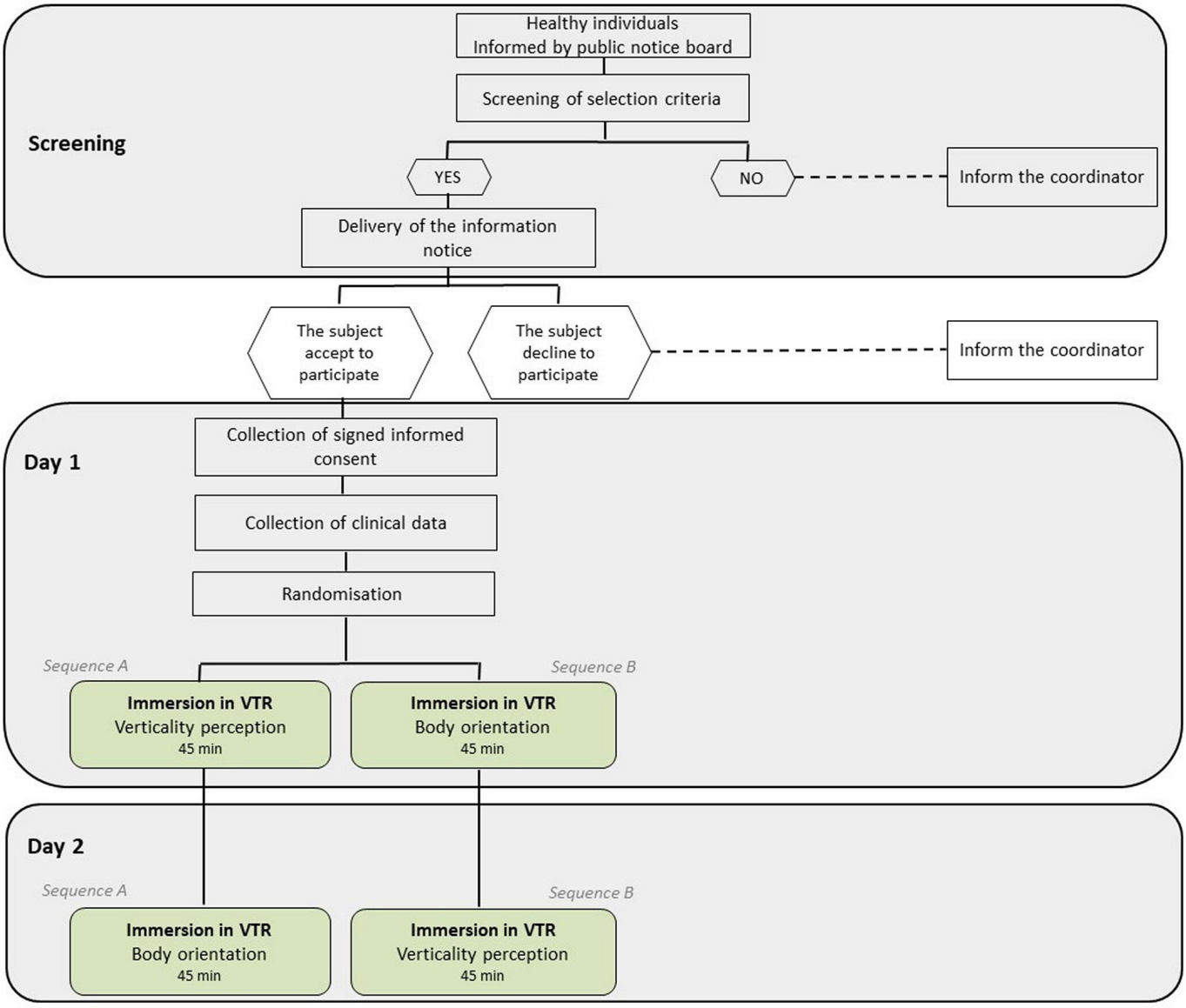

Figure 1 Procedure from enrolment to the end of study for healthy participants. VTR, virtual tilted reality.

orientation and WB distribution). All assessments are performed during the same time frame during the day. By means of a computer-generated randomisation, participants are pseudo-randomly allocated to sequence A (verticality perception on the first half-day (D1); body standing posture on the second half-day (D2)) or sequence B (reverse order). To verify that the VTR effect is symmetrical, half of the healthy participants are immersed in a virtual environment tilted 18° to the right (n=10) and the other half are immersed in a virtual environment tilted 18° to the left (n=10). Assessments and interventions are performed by trained investigators.

Sessions devoted to verticality perception start by a first assessment of PV and VV in darkness, the head-mounted display (HMD) of the VTR worn but in the 'off' setting. Then individuals are immersed in VTR for 15 min, in a seating position, with the instruction to freely explore the immersive virtual environment tilted 18° towards the left or right. They remain immersed in VTR during the second assessment of PV and VV. The second assessment starts after a 15 min immersion in VTR and lasts about 30 min (total duration for PV and VV assessments), which gives a total of 45 min immersion for each session. The existence of a post-effect is searched by additional PV or VV assessments performed 10 min after the VTR arrest, only in participants in whom the VTR induces a change in PV or VV ≥2° (53). During these supplementary PV and VV measurements, participants remain seated in the quiet dark room by wearing a mask covering the eyes and wearing the HMD in the 'off' setting. If present, any post-effect is quantified every 10 min until it disappears.

For the standing posture (active body orientation and WB distribution), measurements are performed under two visual conditions: first in the natural environment (without VTR) and second immersed in the virtual environment (VTR). For each condition, three different instructions are given on how to stand upright, successively: (1) stand comfortably, (2) stand vertical and (3)

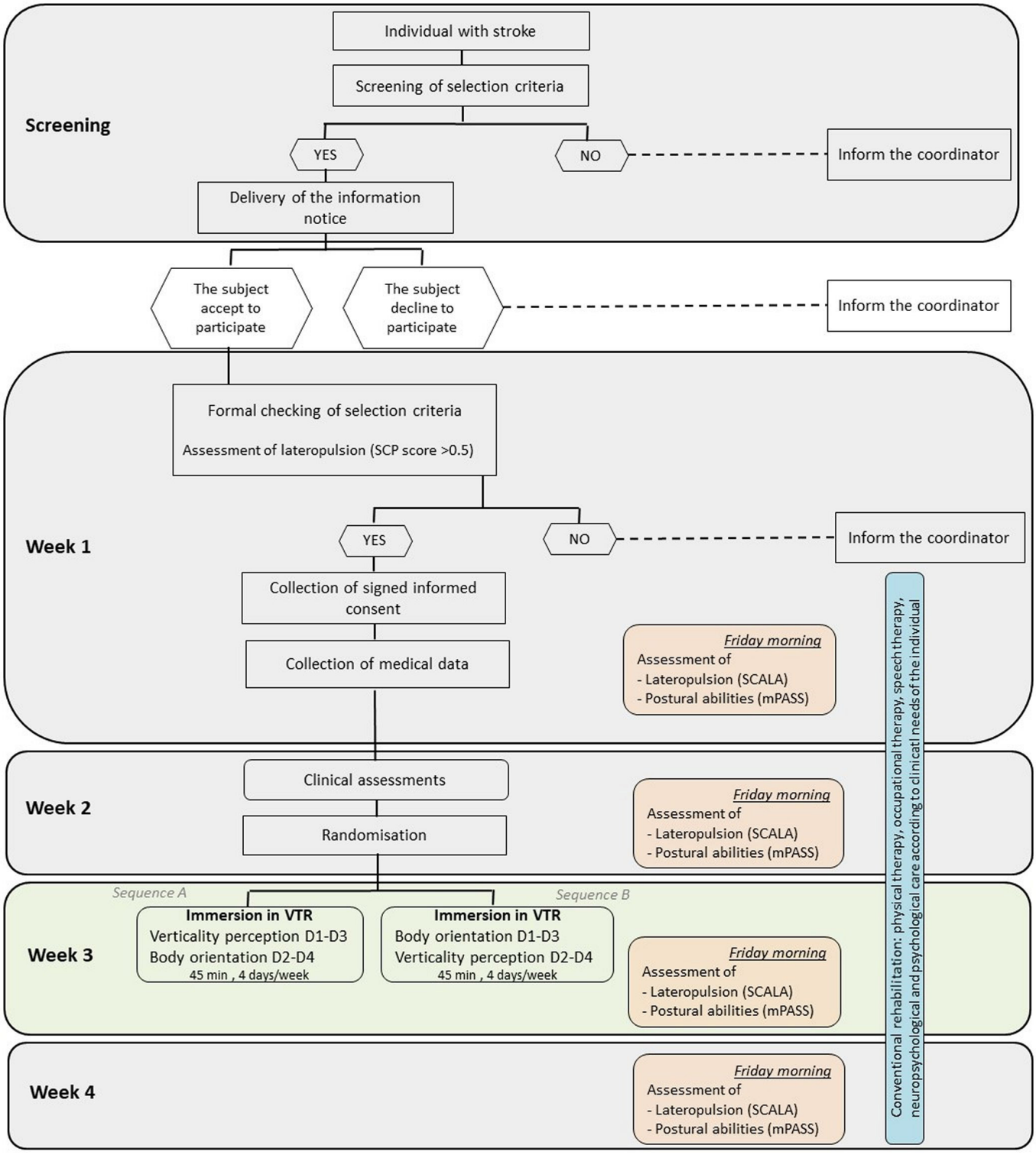

Figure 2 Procedure from enrolment to the end of study for participants with subacute hemispheric stroke. D1–D4, Day 1–Day 4; mPASS: modified Postural Assessment Scale for Stroke;[60 61 72] SCALA, SCAle for LAteropulsion (NCT03077399); SCP, Scale for Contraversive Pushing;[52] VTR, virtual tilted reality.

stand symmetrical with the same weight on each foot. After the baseline assessment in a natural visual environment, participants are immersed in VTR for 15 min, in a seated position, with the instruction to freely explore the immersive virtual environment tilted 18° towards the left or right. They remain immersed for a second assessment of the standing posture (vertical body orientation and WB distribution) with VTR. No VTR post-effect is searched. Instead, we assess participants' awareness of possible changes induced by VTR on body orientation. At the end of each experimental session, we ask participants about any discomfort they experienced

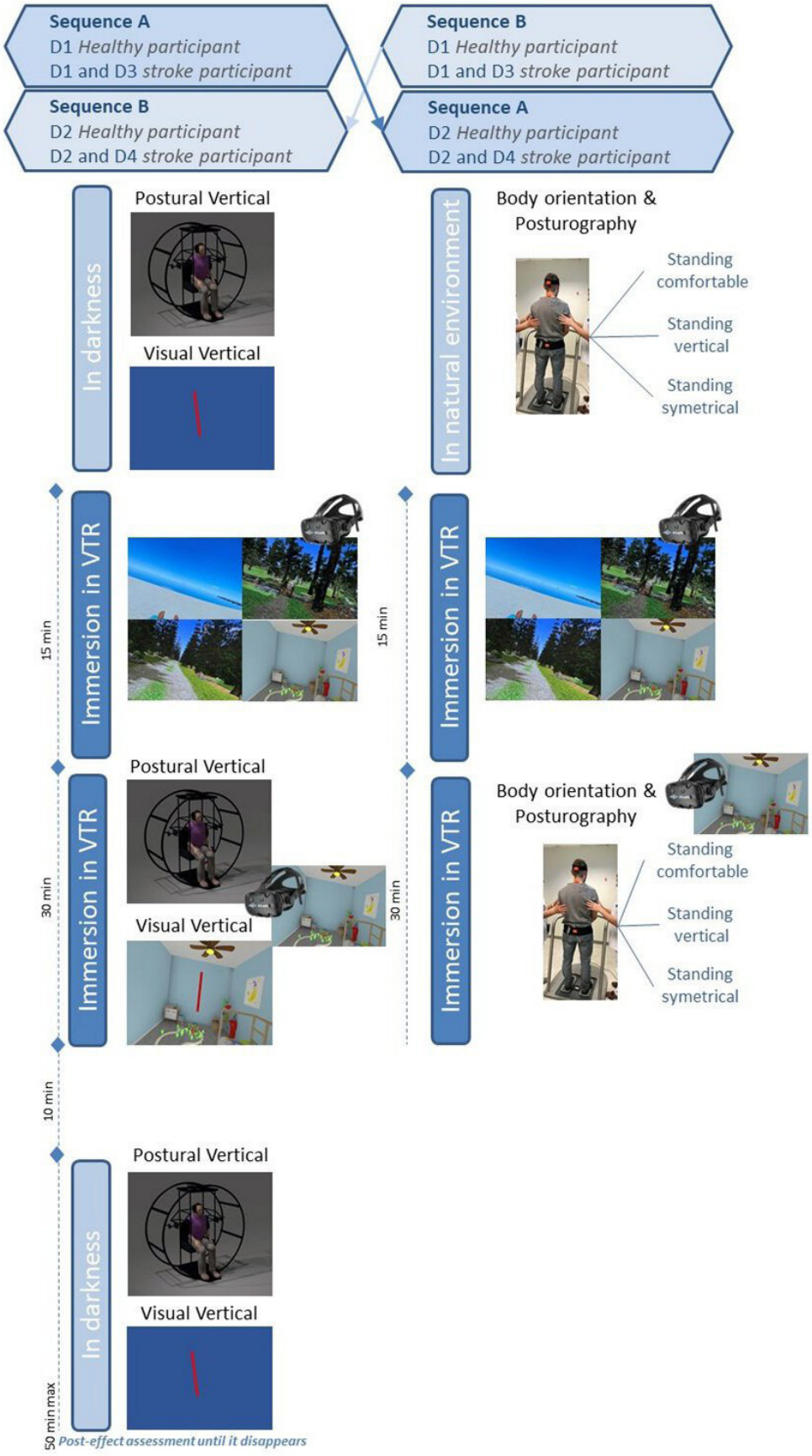

Figure 3 Description of the effect of the virtual tilted reality (VTR) intervention on verticality perception (postural and visual vertical) and standing posture (active body orientation and weight-bearing) for stroke and healthy participants. D1–D4, Day 1–Day 4.

with the VTR immersion (details in online supplemental material).

Individuals with stroke

For individuals with stroke, the study duration is 4 weeks (5 weeks maximum including an optional week in case of a minor medical problem (not related to the protocol) requiring a transitory arrest of the protocol for a few days) with only the third week devoted to the VTR intervention. During the intervention week, four consecutive mornings are devoted solely to the intervention, with no other rehabilitation. In the afternoon, participants continue with their usual rehabilitation, including a physiotherapy session, an occupational therapy session and, if necessary, a speech therapy or neuropsychology session. Outside the experimental week, conventional rehabilitation consists of two sessions/day of physiotherapy (one morning and one afternoon), one session/day of occupational therapy, two–three sessions/week of speech therapy adapted to the deficits, two sessions/week with a neuropsychologist if necessary and one session/week with a psychologist if necessary. The content of conventional rehabilitation sessions is not imposed and is left to the appreciation of therapists, who are not informed of the assessments performed during the study. This content was guided by the deficits and activity limitations. These deficits and limitations may include sitting or standing balance, walking and motor control of the lower and/or upper limbs. Exercises aimed at alleviating rehabilitation are based on evidence and expert opinion[17 20] as well as on basic background.[53] This conventional rehabilitation is associated with an alleviation of the lateropulsion that explains an important part of balance and gait recovery after stroke.[54]

All individuals with a stroke admitted to the rehabilitation department are screened on the basis of their medical records, and their eligibility criteria are checked by a medical physician. Eligible individuals who volunteer to participate then meet with a physical medicine and rehabilitation specialist involved in the study for an inclusion visit to check inclusion/non-inclusion criteria and to sign the informed consent. The week of the inclusion is the first week of the study, labelled 'W1'.

The second week (W2) is devoted to the collection of demographic and individual characteristics and the assessment of clinical deficits using a comprehensive battery of tests. A window of 4 days is allowed to start and complete these assessments. The 3rd week (W3) is devoted to the VTR intervention over four consecutive mornings (D1 to D4, from Monday to Thursday), at the same time of day (figure 3). During the last week (W4), participants follow their conventional rehabilitation programme as in W1 and W2. After these 4 weeks, participants continue their hospital stay according to their clinical needs or return home.

During W3, two mornings are devoted to analysing VTR effects on verticality perception (PV and VV) and two mornings to analysing VTR effects on the standing posture: the active body orientation with respect to gravity on one hand and the WB distribution on the other. To avoid any effects related to learning or fatigue, 10 participants will be pseudo-randomly allocated to the sequence A (verticality perception on D1 and D3; standing posture on D2 and D4) and the 10 others to sequence B in a reverse order (standing posture on D1 and D3; verticality perception on D2 and D4). This randomisation is computer-generated (see details in the specific subsection) and stratified on lateropulsion severity. Sessions for verticality perception assessments and body orientation and WB distribution assessments are similar to those performed in healthy individuals, except that the immersive virtual environment is tilted 18° toward the side opposite their lateropulsion. The post-effect is assessed once for PV during the first session (D1 for sequence A or D2 for sequence B) and once for VV during the second session (D3 for sequence A or D4 for sequence B).

Weekly assessments are performed to assess the possible cumulative effect of VTR sessions on lateropulsion and balance capacities. They are performed every Friday morning, from W1 to W4, by a skilled physiotherapist, with masking to the study hypothesis and timeline.

Randomisation

Participants are randomised during the inclusion phase. The allocation of the sequence's order (A or B) is generated by Ennov Clinical V.8.2. For individuals with a stroke, the randomisation is stratified both according to the side (right or left) of the stroke and the lateropulsion severity (SCP score ≤3 or >3). This list is managed by only four investigators.

Interventions

Immersion in a tilted virtual environment

Participants wear the Oculus Vive Rift DK2 HMD (Oculus, Menlo Park, California, USA), which delivers the virtual environments generated by the software RelaxationVR V.1.0.6 (Virtualis, France) and the VV evaluation module generated by the software PosturoVR V.0.8.3 (Virtualis, France). They wear their usual glasses within the device to correct vision if needed. To avoid effects related to boredom or fatigue during the 15 min immersion phase, we use four different immersive static tilted environments, presented in a fixed order: beach, forest, logging road and child's bedroom (figure 3). The tilted orientation of the scene is fixed to 18° leftward or rightward, the order of magnitude regularly used[27 36 37] because it is considered optimal to induce VV modulation by tilting a visual frame in a dark surrounding,[55] with low uncertainty.[27 36 37] During PV assessment with VTR, the tilted orientation of the scene is specifically stabilised on the earth's vertical regardless of head orientation, owing to the gyrometer of the device. This sensor compensates for head movements induced by the rotation of the wheel during the test so that the orientation of the room stays tilted at 18°. The leftward or rightward direction is pseudo-randomly counterbalanced for the healthy participant group and as

a function of the stroke side otherwise: individuals with a right hemispheric stroke are immersed in a virtual environment tilted rightward (as opposed to contralesional lateropulsion and verticality perception biases), whereas individuals with a left hemispheric stroke are immersed in a virtual environment tilted leftward. The VR HMD is 2160 pixels wide by 1200 pixels high (× 1080×1200 per eye) with a 110° field of view.

Assessment during the VTR immersion is systematically performed in the same visual environment already used,[27] a child's bedroom (see figure 3).

Tasks and assessments

During W3, three tasks are assessed in the frontal plane, PV, VV and the active standing posture by trained investigators familiar with apparatus and procedures used. These assessments are performed in dedicated rooms.

PV is assessed in sitting position, without any time limit or any feedback, with the device and paradigm designed by Pérennou *et al*.[1] Participants are seated restrained in a wheel-like framework, in complete darkness. The wheel is slowly and manually turned, in the frontal plane, by one operator to the right and left sides alternately, between ±15° and ±45°, within a fixed sequence balancing leftward and initial rightward body tilts. Participants are asked to estimate their PV by signalling the whole-body orientation when they feel upright. After two practice trials, 10 estimates are recorded, and results are calculated as their algebraic mean. Consistent with standards, a negative value corresponds to a tilt to the opposite side of the VTR. According to normal ranges for this assessment, (14) PV-orientation is classified as normal (from −2.5° to 2.5°), tilt to the opposite side of the VTR (if <−2.5°) or tilt to the side of the VTR (if >2.5°). We also calculate the PV-uncertainty that corresponds to the within-subject SD of the 10 measures. PV-uncertainty represents the robustness of the internal model of verticality,[56] a variable to be controlled.

VV is assessed in a sitting position, without any time limit or any feedback, the head and trunk remaining upright,[57] after 2 min spent in darkness (HMD worn but in the 'off' setting). The task previously described[27] consists of binocular visual adjustments of the direction of a bright line presented on a dark blue background without visual clues or on VTR (experimental condition). The participants wear the device (see above) and are asked to set the line to the vertical by giving verbal instructions to the examiner. The initial orientation of the line is randomly determined within a range from ±5° to ±30°, within a fixed sequence balancing leftward and rightward initial tilts of the line. 10 estimates are recorded after two practice trials to reach a robust result.[58] VV-orientation is calculated as for PV-orientation, with normal ranges similar to those described above for PV.[1] We also calculate VV-uncertainty, a variable to be controlled (see PV).

*The standing task consists of actively maintaining the standing position for 20*s without any help, with the participant in socks (with no shoes or orthoses) and feet positioned parallel on marks drawn on two platforms, 14 cm apart, which corresponds approximately to the spontaneous posture adopted by humans in quiet standing. Participants are instructed to remain as still as possible with their arms hanging by their sides, without talking and looking straight ahead. For safety reasons, these sessions are conducted by two operators, and participants stand within a handrail shaped around the platforms (front and sides), with a chair behind them. They are helped to stand up from this chair and sit down for a rest at any time if needed. Three different instructions on how to stand upright are successively given in the same order, per block of four trials of 20 s each: (1) stand comfortably, (2) stand vertical, then (3) stand symmetrical by distributing the weight equally between the two lower limbs. This gives a total of 24 trials, 12 before the VTR in the natural visual environment of the room and 12 during the VTR (details in online supplemental material). The body orientation (head, trunk and pelvis) in the frontal plane and the WB distribution are simultaneously recorded by three inertial measurement units (Xsens Awinda motion sensors; Xsens, Enschede, The Netherlands), and one dual-force platform device for posturography (Feetest6, Techno Concept, Manosque, France). Body orientation is quantified for each trial, then averaged for each of six conditions: standing comfortable, vertical or symmetrical, before and during the VTR. Head, trunk and pelvis orientations (head-orient, trunk-orient and pelvis-orient) are measured by three Xsens sensors positioned by band straps on the skin: over the occipital apex, the C7 spinous process and the L5–S1 spinous process (figure 4). Sensors are positioned and calibrated when the participant is in an upright sitting position, maintained by therapists (figure 4). Head-orient, trunk-orient and pelvis-orient are recorded with a frequency of 100 Hz. The mean values (in degrees) of the four trials of 20 s each are calculated for each condition. A negative value corresponds to a tilt to the opposite side of the VTR, so the paretic side for individuals with a stroke. The WB distribution is quantified by the proportion of body weight supported by the lower limb opposite to the side of the VTR. We also extract as a controlled variable the amount of sway, corresponding to 2 SD of the mediolateral position of the centre of pressure (in mm). Details on the metrologic features of the posturographic device and parameters are given elsewhere.[59]

Lateropulsion and balance abilities are assessed each Friday morning for 4 weeks. We will monitor lateropulsion course with the SCAle for LAteropulsion (SCALA). For inclusion, we quantify lateropulsion with the SCP, but its responsiveness is not sufficient to capture weekly changes.[54] The SCALA is a novel scale for assessing post-stroke lateropulsion (ClinicalTrial.gov NCT03077399). The SCALA has been designed to detect and quantify all forms of lateropulsion, contraversive and ipsiversive post-stroke lateropulsion, regardless of their mechanisms and stroke side, including mild forms and those attenuated after rehabilitation. Its content validity has been finalised by a Delphi process with a panel of international experts (

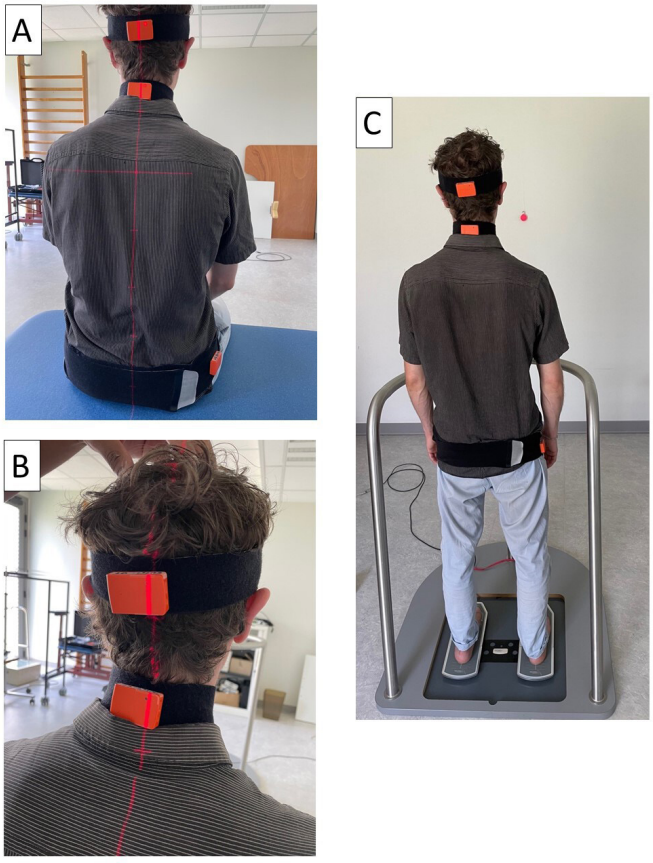

Figure 4 Illustration of the three motion sensors positioned on the head (occipital apex), trunk (C7 spinous process) and pelvis (L5–S1 spinous process). Part A and B illustrate the sensor positioning and calibration in a sitting position. Part C illustrates the sensor positioning in a standing position.

Table 1 Summary of clinical and experimental assessments at each time point for healthy participants

	D1 (sequence A) or D2 (sequence B)	D2 (sequence A) or D1 (sequence B)
Medical information	X	
Inclusion		
Age	X	
Sex	X	
Height	X	
Weight	X	
BMI	X	
Handedness	X	
Verticality perception		
Postural vertical (PV)	X	
Visual vertical (VV)	X	
Body orientation in frontal plane		X
Standing posturography		X
Awareness of body orientation changes under VTR		X
Discomfort associated with the immersion in VTR	X	X
Adverse events	X	X

BMI, body mass index; D1–D2, Day 1–Day 2; VTR, virtual tilted reality.

ClinicalTrial.gov NCT03077399). The SCALA rates four domains: spontaneous lateral body tilt in tasks of erect postures of increasing difficulty (maintain/change; sitting/standing; feet apart/together; eyes open/close), its anosognosia, self-initiated lateral pushing and resistance to passive corrections. The monocentric study for assessing its reliability and validity has been completed (ClinicalTrial.gov NCT03077399). Results show that the SCALA has good reliability and internal consistency, without floor or ceiling effects. The articles are in preparation. The SCALA-V1 used in the VIRGIL study is provided in additional material; its total score ranges from 0 to 50. The higher the score, the more severe the lateropulsion. Balance abilities in daily life are assessed by a modified version of the Postural Assessment Scale for Stroke (mPASS). The mPASS has been proposed to enhance the PASS, to meet the conclusions of a systematic review of its clinimetrics (PROSPERO registration CRD42021229497), presented in a medical thesis[60] and being currently updated for publication. In particular, the mPASS takes into account the conclusion of two Rasch analyses that confirmed the wide spectrum of postural control levels captured by the PASS but also pointed out an insufficient representation of higher levels of postural control.[61] The mPASS comprises five new items appropriate to detect troubles in individuals with mild asymmetric post-stroke deficits and better cover postural abilities in standing, leading to a total score from 0 to 50. The higher the score, the better the balance abilities in daily life. The five new items are turn around 360° on the paretic side, turn around 360° on the healthy side, stand on tiptoe, tandem stance and standing with feet together, eyes closed and head in extension.

Demographics and clinical features of participants are in tables 1 and 2. Table 1 lists clinical data extracted from interviews with healthy participants as well as the summary of assessments at each time point. Table 2 lists clinical data systemically collected in our clinical practice for participants with stroke and for the study extracted from medical records (details in online supplemental material) as well as the summary of assessments at each time point. The clinical profile of responders will be analysed (nature and severity of deficits, localisation and size of stroke lesion). Lesion location and stroke volume are determined on the basis of the brain anatomical MRI performed for clinical needs at about 2 months post-stroke. Details of MRI analyses are described in online supplemental material.

Table 2 Summary of clinical and experimental assessments at each time point for participants with a stroke

	Study period			
	W1	W2	W3	W4
Medical information	X			
Eligibility criteria				
Lateropulsion (SCP)[52]	X			
Aphasia (ASRS)[73]	X			
Depression (ADRS)[74]	X			
Inclusion				
Age	X			
Sex	X			
Height	X			
Weight	X			
BMI	X			
Clinical assessments				
Motor weakness		X		
Sensibility		X		
Spasticity		X		
Gait		X		
Hemianopia		X		
Apraxia		X		
Spatial neglect		X		
Handedness		X		
Verticality perception				
Postural vertical (PV)			X	
Visual vertical (VV)			X *2 mornings/week*	
Body orientation in frontal plane			X	
Standing posturography			X	
Awareness of body orientation changes under VTR			X *2 mornings/week*	
Discomfort associated with the immersion in VTR			X *4 mornings/week* *After each VTR session*	
Lateropulsion (SCALA)	X *Friday morning*	X *Friday morning*	X *Friday morning*	X *Friday morning*
Postural abilities (mPASS)[60 61]	X *Friday morning*	X *Friday morning*	X *Friday morning*	X *Friday morning*
Brain MRI	About 2 months post-stroke			
Adverse events	X	X	X	X

ADRS, Aphasia Rating Scale; ASRS, gravity section score of the French version of the Goodglass & Kaplan Aphasia Severity Rating Scale; BMI, body mass index; mPASS, modified Postural Assessment Scale for Stroke; SCALA, SCAle for LAteropulsion (NCT03077399); SCP, Scale for Contraversive Pushing; VTR, virtual tilted reality; W1–W2–W3–W4, Weeks 1–2–3–4.

Outcomes

Primary outcome

The primary outcome is the change in PV-orientation (°) induced during the VTR. It is calculated by subtracting the PV-orientation during VTR from the PV-orientation at baseline. A positive value indicates PV modulation towards the VTR, and a negative value indicates PV modulation in the direction opposite to the VTR.

PV-uncertainty corresponds to the within-subject SD of the 10 measures[56] and is monitored to ensure that there are no problems during the test. Uncertainty <3° indicates robust results of orientation.

Secondary outcomes related to verticality perception

Change in VV-orientation (°) is a secondary outcome, calculated as for PV-orientation. VV-uncertainty is also monitored to ensure robust results of orientation.

A post-effect on PV and VV orientations is calculated by subtracting the orientation 10 min after VTR from the orientation at baseline. A responder is an individual with a modulation of PV-orientation ≥2° towards the VTR side during VTR. The proportion of responders and their clinical characteristics (nature and severity of the deficits, localisation and size of stroke lesion) are analysed.

Secondary outcomes related to the active body orientation in standing

Change in head-orient, trunk-orient and pelvis-orient (°) under VTR immersion is calculated by subtracting the orientations during VTR (°) from the orientations at baseline (°). A positive value indicates a body orientation modulated towards the VTR, and a negative value indicates a body orientation modulated in the direction opposite to the VTR.

The cumulative effect of the W3 VTR sessions on the lateropulsion severity of individuals with a stroke and its corollary balance abilities is calculated by the SCALA-V1 (score/50) and mPASS (score/50 points).

Awareness of body orientation changes under VTR immersion is assessed with a 5-point ad hoc Likert scale ranging from −2 to +2 by interviewing participants after the task actively maintaining the standing posture and then averaged. A score of 0 corresponds to the feeling that body orientation did not change during the VTR immersion. A score of −2 corresponds for healthy participants to the feeling of being tilted a lot toward the left side and for stroke participants to the feeling of being much more tilted (more severe lateropulsion). A score of +2 corresponds for healthy participants to the feeling of being tilted a lot toward the right side and for stroke participants to the feeling of being much less tilted (less severe lateropulsion).

Secondary outcomes related to the WB criterion

Change in WB induced by the VTR is obtained by the WB difference before and during VTR. A positive value (% of body weight) indicates that the VTR unloads the opposite lower limb and loads the lower limb at the side of the VTR and vice versa for a negative value. WB differences are analysed between the three instructions to stand (comfortable, vertical, symmetrical). The association between the trunk orientation (°) in the frontal plane and WB at baseline and during VTR is also analysed.

Discomfort associated with VTR immersion

Discomfort is assessed by a visual analogue scale score ranging from 0 (no discomfort) to 10 (intolerable discomfort) by participants after each session of VTR immersion (two times for healthy participants and four times for stroke participants). Moreover, participants are asked to report any discomfort and adverse somatic effects (eg, headaches, dizziness, vomiting and nausea), which will be subjected to a qualitative analysis. Major discomfort, a priori defined by a visual analogue scale score ≥5 or the existence of somatic manifestations (dizziness or nausea, etc), is a criterion for discontinuing the experimental session.

Sample size

This pilot study is the first within-person randomised trial assessing VTR effects on PV in individuals tested at the subacute stage after a hemispheric stroke. Because PV is the primary outcome of the study, we cannot calculate a theoretical sample size. On the basis of previous studies attempting to experimentally modulate PV tested with the same device and paradigm as the current study,[22 27 51] we estimated a high chance of concluding by recruiting 20 healthy individuals and 20 individuals exhibiting lateropulsion after a hemispheric stroke.

Statistical analyses

Categorical variables will be analysed by number (%) and continuous variables by mean (SD) or median (IQR) as appropriate. Variable distribution will be graphically checked, and normality will be assessed with the Shapiro-Wilk test. Baseline characteristics will be compared between groups (stroke and healthy participants) by Fisher's exact test or χ^2 test for categorical variables and independent Student t-test for continuous measures (or Mann-Whitney test for variables with non-normal distribution). We will use two-sided $p \leq 0.05$ for statistical significance.

Unadjusted means and SEs will be estimated for all continuous outcomes. Linear mixed-effect models will be created with different factors/covariates according to objectives previously stated: time (before/after or endpoint assessments according to outcomes) and sessions (1–4) as within-participant factors, and group (stroke participants and healthy participants) as a between-participant factor. Different interactions will be examined according to objectives. The side of the stroke lesion (right or left) and the severity of lateropulsion (SCP score ≤3 or >3), two variables that are stratified in the randomisation, as well as the assessment sequence (A–B or B–A; figure 2) will be tested as covariates in models as appropriate. Time, sessions, group, the side of stroke lesion and lateropulsion severity will be considered as fixed factors in models and participants and the assessment sequence as random factors. Post hoc tests will be performed according to objectives previously stated, and multiple comparisons will be adjusted by using the Bonferroni-like method. If a Gaussian distribution cannot be assumed, generalised mixed-effects models could be used with other types of distribution as appropriate. Otherwise, data transformations or non-parametric tests

will be implemented. Intention-to-treat analyses will be performed. Missing data will be handled by mixed-effect models. For secondary outcomes, per protocol analyses could be used.

The correlation between changes induced by VTR on verticality perception and those on the postural behaviour will also be analysed by linear mixed-effects regression including group and time as covariates. For stroke participants, we will compare stroke lesion characteristics and clinical deficits of responders to the VTR (modulation of PV ≥2°) to those of non-responders (modulation of PV <2°). We will use Fisher's exact or χ^2 test for categorical data and independent Student t-test for continuous data (or Mann-Whitney test).

Patient and public involvement

None.

ETHICS AND DISSEMINATION

The study is promoted by the Grenoble-Alpes University Hospital and was approved by an institutional review board randomly selected at a national level (Comité de Protection des Personnes Ile de France X; 2020-A02941-38, amendment 2024). It was registered on ClinicalTrials.gov before any participant inclusion (NCT04911738). The trial is performed in accordance with the Helsinki Declaration. Before inclusion, information related to the study is given to eligible participants. After a reflection time of at least 24 hours, individuals agreeing to participate sign a free and informed consent (online supplemental material). All participants remain free to discontinue their participation in the trial, at any time. Procedures to collect and store personal data are in accordance with the General Data Protection Regulation of the European Union and have been declared to the French committee for data protection, the Commission nationale de l'informatique et des libertés (CNIL), in accordance with French laws and regulations.

Any potential important modification to the protocol that may affect the conduct of the study, potential benefit of the participant or participant safety, including changes of study objectives, study design, population, sample sizes, study procedures or significant administrative aspects, will require a formal amendment to the protocol. This amendment will be submitted for approval to this institutional review board before implementation.

Participants will not have to support any cost related to their participation in the study. Healthy participants are entitled to a participation allowance of €50 to cover travel expenses. Stroke participants receive conventional rehabilitation in accordance with current practices and their personal clinical needs. The risk for participants is considered low. All assessments are painless and non-invasive. Virtual reality is generally well tolerated by individuals, but some adverse effects, known as 'virtual reality sickness', have been reported.[62] Although headaches, nausea and dizziness are rare and of low intensity,[63–66] this risk is attenuated in our study by the use of up-to-date virtual reality technology. This is the only expected adverse effect of the trial. Moreover, in our study, an adverse event is defined as any untoward medical occurrence in a participant without regard to the possibility of a causal relationship. Adverse events are collected after the participant has provided consent and is enrolled in the study. An adverse event that meets the criteria for a serious adverse event between study enrolment and hospital discharge is reported to the local institutional review board.

Details on data management and monitoring are reported in online supplemental material. Anonymised data that support the findings of this study are available from the corresponding author, on reasonable request, only for authorised research. Their use is subject to an agreement with the promotor (CHU Grenoble Alpes) and the principal investigator (Pr Dominic Pérennou) of the VIRGIL study. Pseudonymised data that support the findings of this study are available from the promotor (CHU Grenoble Alpes) on reasonable request, subject to a specific agreement with the promotor (involving the principal investigator) and subject to regulatory proceedings due to data protection applicable laws. Access conditions are to be determined depending on the nature of the request.

DISCUSSION

The main purposes of this pilot study are (1) to explore in healthy individuals the VTR effects on perception, representations and actions referred to verticality to better understand how the brain constructs and updates the internal model of verticality and, if needed, adopts a compromise between the control of body orientation with respect to gravity and the control of WB, and (2) to investigate in individuals with hemispheric stroke whether VTR could be an effective rehabilitation tool to alleviate lateropulsion caused by a biased verticality representation and so improve balance ability. PV is the primary outcome, because to our knowledge no study has ever investigated a VTR effect on the postural modality of verticality perception, the strongest modality associated with postural orientation with respect to gravity and postural disorders.[1] An approach restricted to one modality does not guarantee a modulation at a high level of representation but can only reflect a perceptual effect. We assume that modulating the active body orientation requires modulating the internal verticality representation, not just the perception of one modality. Therefore, we analyse the modulation by VTR of both PV and VV perceptions, along with perception of the body orientation in the frontal plane. We also assume that the body tilt is the cardinal sign of lateropulsion,[3 18] which has rarely been quantified by an instrumental measure.[42] We analyse the head, trunk and pelvis orientations in the frontal plane. Many individuals with a hemisphere stroke unload the paretic lower limb, which is considered a complex postural behaviour

resulting from several causes, including sensorimotor deficits bearing on the paretic lower limb and biases in spatial representation.[25 67–70] It might also result from a compromise between the control of the body orientation with respect to gravity and control of the postural stabilisation on the ground.[59 71] Only one experimental study has documented this possibility,[71] showing that the paretic lower limb is loaded when lateropulsion is alleviated by a support for the upper limb. Therefore, in our study, we will analyse the covariations between the trunk orientation quantified by an inertial sensor and the WB quantified by posturography in several visual conditions (before and during VTR) as well as for several instructions to stand (comfortable, vertical, symmetrical), both in healthy individuals and individuals tested at the subacute phase after a hemispheric stroke.

Virtual reality allows for full immersion in virtual spaces with a large-scale frame and structurally meaningful three-dimensional. It is a mobile, safe and non-invasive rehabilitation tool, increasing in accessibility in terms of equipment cost, and presents numerous benefits versus classical rehabilitation. It allows for customising sessions, helping therapists motivate post-stroke individuals to stay engaged in rehabilitation, especially individuals with stroke who often present attentional cognitive deficits. Also, it can be delivered both in individuals in acute, subacute and chronic stages of stroke, with light or severe deficits. More specifically, for post-stroke lateropulsion rehabilitation, it allows for easily implementing immersion in a tilted environment by easily manipulating a visual frame of reference. Hence, it could be an effective complement to conventional rehabilitation for lateropulsion.

The first limitation is that this is a pilot study with an exploratory design that does not allow for calculating sample size. This sample size was estimated from previous experimental studies modulating verticality perception. The sample size is small, and for this difficult experiment, we will have to select participants with stroke on the basis of their lateropulsion (not too light, not too severe) as well as their physical and cognitive capacities and medical stability. This selection will attenuate the generalisation of results. This study uses a prototype to evaluate the VP, which could limit its replication.

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