PLOS ONE

Human-Prosthetic Interaction (HumanIT): A study protocol for a clinical trial evaluating brain neuroplasticity and functional performance after lower limb loss

Elke Lathouwers[1,2], Bruno Tassignon[1], Alexandre Maricot[1], Ahmed Radwan[3],
Maarten Naeyaert[4], Hubert Raeymaekers[4], Peter Van Schuerbeek[4], Stefan Sunaert[3,5],
Johan De Mey[4], Kevin De Pauw[1,2,6] *

1 Human Physiology and Sports Physiotherapy research group, Vrije Universiteit Brussel, Brussels, Belgium,
2 BruBotics, Vrije Universiteit Brussel, Brussels, Belgium, 3 KU Leuven, Department of Imaging and
pathology, Translational MRI, Leuven, Belgium, 4 Department of Radiology and Magnetic Resonance, UZ
Brussel, Jette, Belgium, 5 UZ Leuven, Department of Radiology, Leuven, Belgium, 6 Strategic Research
Program 'Exercise and the Brain in Health & Disease: The Added Value of Human-Centered Robotics', Vrije
Universiteit Brussel, Brussels, Belgium

* Kevin.De.Pauw@vub.be

Abstract

Background

Lower limb amputation contributes to structural and functional brain alterations, adversely
affecting gait, balance, and overall quality of life. Therefore, selecting an appropriate pros-
thetic ankle is critical in enhancing the well-being of these individuals. Despite the availability
of various prostheses, their impact on brain neuroplasticity remains poorly understood.

Objectives

The primary objective is to examine differences in the degree of brain neuroplasticity using
magnetic resonance imaging (MRI) between individuals wearing a new passive ankle pros-
thesis with an articulated ankle joint and a standard passive prosthesis, and to examine
changes in brain neuroplasticity within these two prosthetic groups. The second objective is
to investigate the influence of prosthetic type on walking performance and quality of life. The
final objective is to determine whether the type of prosthesis induces differences in the walk-
ing movement pattern.

Methods

Participants with a unilateral transtibial amputation will follow a 24-week protocol. Prior to
rehabilitation, baseline MRI scans will be performed, followed by allocation to the interven-
tion arms and commencement of rehabilitation. After 12 weeks, baseline functional perfor-
mance tests and a quality of life questionnaire will be administered. At the end of the 24-
week period, participants will undergo the same MRI scans, functional performance tests

and questionnaire to evaluate any changes. A control group of able-bodied individuals will be included for comparative analysis.

Conclusion

This study aims to unravel the differences in brain neuroplasticity and prosthesis type in patients with a unilateral transtibial amputation and provide insights into the therapeutic benefits of prosthetic devices. The findings could validate the therapeutic benefits of more advanced lower limb prostheses, potentially leading to a societal impact ultimately improving the quality of life for individuals with lower limb amputation.

Trial registration

NCT05818410 (Clinicaltrials.gov).

Introduction

A lower limb amputation is a life-altering event that significantly affects an individual's overall well-being or quality of life due to the loss of mobility, physical strains and psychosocial impacts [1, 2]. The absence of a limb restricts the individual's ability to perform daily tasks, leading to physical discomfort, secondary injuries and a higher risk of falling [3–7]. A recent review indicates that 54% of the people with a lower limb amputation wearing a standard passive prosthesis reported falling in the last year, with 26% reporting falling multiple times [7]. On top, it is estimated that 60% of these falls require medical attention [8, 9]. Falls can result in additional injuries, further impairing mobility and independence and increasing fall-related healthcare costs [7, 9, 10]. Addressing these challenges is crucial to improving overall well-being and enhancing the individual's quality of life.

The brain is often overlooked when discussing the effects of amputation. Even though, after an amputation, significant structural and functional neuroplastic changes occur, contributing to decreased static and dynamic balance, increased gait variability and an increased **risk of falling** [7, 11, 12]. Gait patterns and the onset of falls are orchestrated by the intricate interplay between biomechanical factors and the human brain [13]. This interaction entails that the brain plays a vital role in the organisation and performance of human gait [13]. Magnetic resonance imaging (MRI) revealed that lower limb amputation contributes to the thinning of the premotor cortex and visual-motor area, the reduction in white matter integrity within the premotor region contralateral to the amputation site, along with changes in the connectivity between bilateral premotor cortices [12]. These changes disrupt the processes involved in movement planning and the coordination of eye movements relative to the limbs, resulting in reduced perception-action coupling [12]. In addition, amputation influences changes in limb representation in the primary motor and somatosensory cortex. It induces decreased connectivity in the primary motor cortex, primary somatosensory cortex, supplementary motor area, basal ganglia, thalamus, and cerebellum [12]. These changes in connectivity translate towards reduced motor control and balance, further complicating the performance of daily activities of people with lower limb amputation [12].

Given the challenges posed by these neurological changes, enhancing the quality of life for people with amputation necessitates the use of suitable prosthetic ankle devices. Today, passive devices are among the prosthetic feet most widely used [14]. The majority of passive mechanical prostheses rely on a fixed spring, are not articulated and offer basic functionality [14]. To

better mimic able-bodied gait, articulated ankle joints are integrated into such passive devices, enhancing biomechanical factors and increasing the quality of life (e.g. increased mobility, comfort and gait patterns) [14–16]. Yet, there is insufficient evidence for their beneficial influence on brain neuroplasticity [17].

Understanding the influence of passive and articulated passive prostheses on brain neuroplasticity will provide vital information on the underlying mechanisms in the context of fitting an individual with amputation with the most beneficial prosthetic device to improve functionality, reduce fall risk and ultimately improve quality of life. A recent systematic review compared the therapeutic benefits of different ankle prostheses (i.e., passive, quasi-passive and active) during daily activities [17]. This review demonstrated that although many short-term benefits of advanced prosthetic devices have been shown through user evaluations, there is a lack in the literature concerning mid-to-long-term holistic assessments employing a psycho-physiological approach [17]. Furthermore, among the included manuscripts, only De Pauw et al. investigated the difference in brain dynamics between two types of prosthetic ankles by means of EEG [18]. Nevertheless, research on the impact of the prosthesis type on neuroplasticity is notably absent from scientific literature. Therefore, our study aims to research brain neuroplasticity induced by different types of prosthetic ankle devices.

Objectives

The primary objective is to examine the differences in the degree of brain neuroplasticity using magnetic resonance imaging (MRI) between individuals wearing a new passive ankle prosthesis with an articulated ankle joint and a standard passive prosthesis, and to examine changes in brain neuroplasticity within these two prosthetic groups. We hypothesise that the neuroplastic changes influenced by the amputation will be less pronounced in people using an articulated prosthesis than those using a standard passive device. The secondary objective is to investigate walking performance and quality of life related to the type of prosthesis. We hypothesise that walking performance and quality of life will increase when using the prosthesis with an articulated ankle joint. The final objective is to determine whether the type of prosthesis induces differences in the walking movement pattern in individuals with a unilateral lower limb amputation. We hypothesise that movement patterns will more closely align with able-bodied gait patterns in individuals wearing the prosthesis with an articulated ankle joint compared to those wearing the standard passive device.

Materials and methods

The study protocol has been reported in compliance with the SPIRIT 2013 guidelines [19]. The World Health Organization trial registration data is presented in S1 Table. The completed SPIRIT 2013 checklist and the original protocol are also provided as supporting information.

Study design & sample size

The study has been designed as a controlled clinical trial with three parallel study arms. Given the nature of the research involving distinct prostheses, neither participant nor investigator blinding is possible. Fig 1 shows a diagram with the different phases of the study. Participants with a unilateral transtibial amputation will be allocated to one of the two prosthetic study arms (i.e. standard care prosthesis vs new articulated prosthesis) with alternate (1:1) allocation. The primary endpoints of the clinical trial are the differences in brain neuroplasticity and the distance covered during the 6-minutes' walk test between the prosthetic arms. With this study being the first to investigate brain neuroplasticity in relation to the type of prosthesis, data to conduct sample size estimation is lacking. Therefore, the sample size for this study was
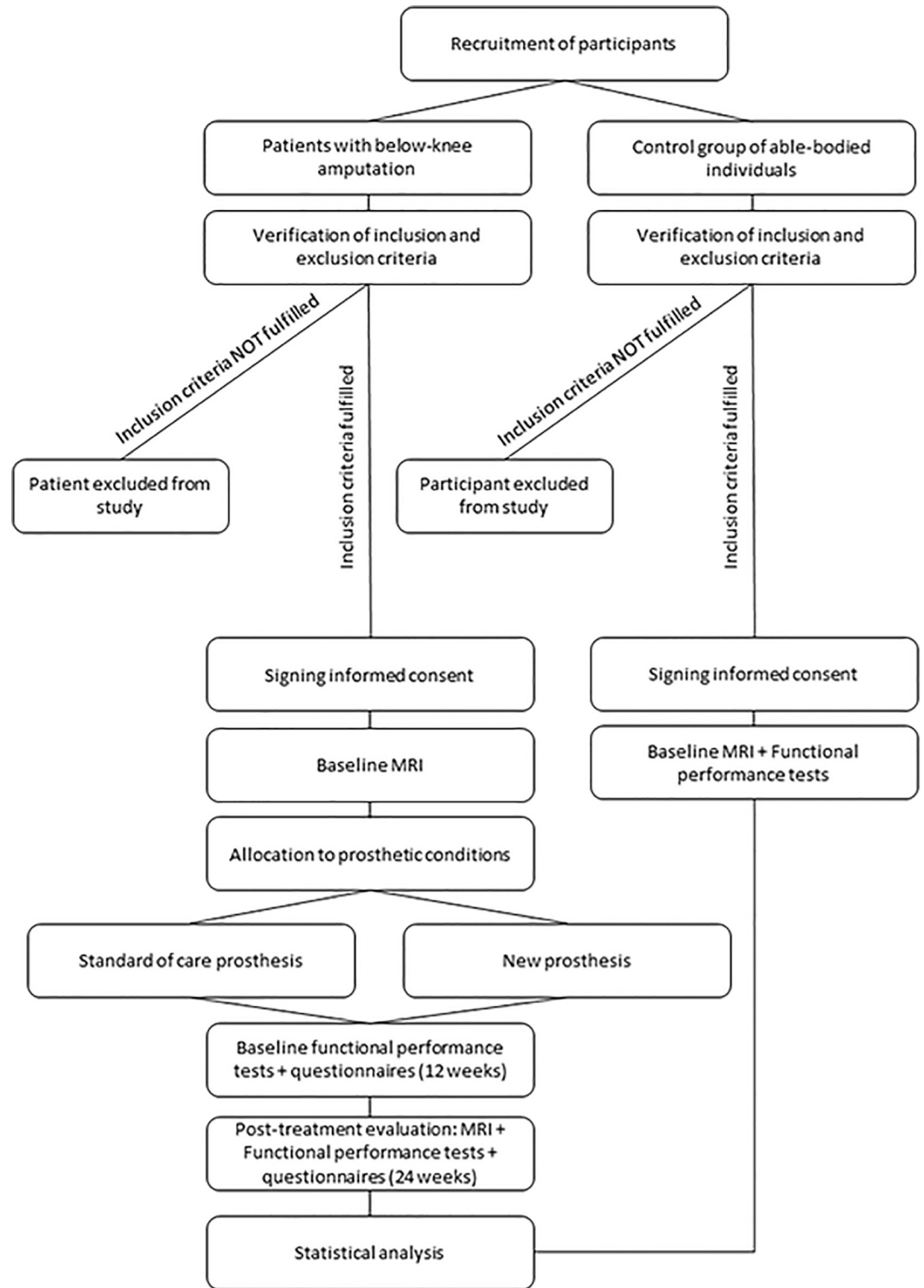
Fig 1. Study flowchart.

https://doi.org/10.1371/journal.pone.0299869.g001

calculated based on the data available for the distance covered during the 6-minutes' walk test [20]. We performed a sample size calculation for an analysis of variance using G*Power (version 3.1.9.4) envisaging 10% drop-out. Values used for this calculation were medium expected effect size f = 0.318, power = 0.80, alfa = 0.05, the number of groups = 3 and the number of measurements set at 2 with a correlation between measurements of 0.75. A total of 40 participants with a lower limb amputation is required and will be allocated alternatingly (i.e., pseudo-randomisation) to one of the two prosthetic groups. A control-group of 20 able-bodied individuals will be included to a third study arm to enable comparison.

Inclusion and exclusion criteria

Adults aged 25–65 with a unilateral transtibial amputation will be recruited through four rehabilitation centres, and orthopaedic departments of hospitals in Belgium. Recruitment will take place from September 2023 onwards until the required sample size is attained. Adults with a Medicare Functional Classification level < K3, metal implants, bilateral amputation, additional upper-limb amputation or diabetes and participants with neurological disorders or excessive stump pains and wounds will be excluded. All participants will be asked to provide their written consent after being written and verbally informed regarding the study protocol. The study will be executed in compliance with the Declaration of Helsinki [21] and is approved by the medical ethics commission of VUB and UZ Brussel (BUN 1432023000077). The study is registered via Clinical.trials.gov (NCT05818410).

Protocol

We will compare a new passive articulated prosthetic ankle-foot (Lunaris®) to a conventional non-articulated prosthetic foot (SACH®) on brain neuroplasticity, functional physical performance, quality of life and movement patterns by means of a clinical trial.

The clinical trial will comprise four test days for participants with a lower limb amputation and two days for the control group of able-bodied individuals. The able-bodied individuals will undergo an MRI-scan at the University hospital Brussels followed by functional performance tests conducted.

Participants with a lower limb amputation will start the clinical trial upon the start of their rehabilitation. The rehabilitation will be provided by the patients their physiotherapist of choice and is not part of this trial. At week 0, when initiating the rehabilitation, participants will undergo a baseline MRI-scan at the University hospital Brussels. Then, they will be allocated alternatingly to the intervention arms (new articulated ankle-foot prosthesis or standard foot prosthesis) and will conduct their rehabilitation to learn walking with a prosthesis. At the end of the rehabilitation, at 12 weeks, participants will perform baseline functional performance tests, and fill out the prosthetic evaluation questionnaire measuring quality of life [22]. Between weeks 12 and 24 of the clinical trial, participants will perform their daily activities with their allocated prosthesis. During this 12-week period, trying out new prosthetic devices will be allowed within the group of individuals wearing the standard prosthetic foot as this is considered the usual care. At the end of this period (at week 24), post-intervention assessments will take place and participants will undergo the same MRI and functional performance tests and fill out the same quality of life questionnaire to evaluate the changes that occurred. Additionally, participants will be asked to fill out the Quebec User Evaluation of Satisfaction with Assistive Technology to evaluate their prosthetic satisfaction [23, 24]. The 12-week intervention period is chosen based on studies examining the effect of 12 weeks balance training in healthy and older adults on neuroplasticity and on the accommodation time to walking with a new prosthesis [25–27]. Throughout the study, the time during which the individuals walked

	STUDY PERIOD				
	Enrolment	Allocation	Post-allocation		
TIMEPOINT**	- Week 0	Week 0	Week 0	Week 12	Week 24
ENROLMENT					
Eligibility screen	X				
Informed consent	X				
Allocation		X			
TREATMENT					
New articulated passive ankle-foot prosthesis	X	X	X	X	X
Standard foot prosthesis	X	X	X	X	X
Able-bodied individuals	X	■	X	■	■
ASSESSMENTS					
Brain neuroplasticity			X	■	X
Quality of life			■	X	X
Prosthetic satisfaction			■	■	X
Functional performance & questionnaires			X*	X	X

Fig 2. The schedule of enrolment, interventions, and assessments. *only for able-bodied individuals.

https://doi.org/10.1371/journal.pone.0299869.g002

with their prosthetic device over the 24h period will be estimated based on anamnestic questions on the average hours of prosthetic use a day, duration and frequency of rehabilitation period. Fig 2 presents an overview of the schedule of enrolment, interventions, and assessments.

Auxiliary subject information and outcome parameters

An overview of the different outcome parameters is provided in Table 1.

Auxiliary subject information. Auxiliary subject information will be collected during the first day of data collection for the participants with an amputation. The subject information that will be collected comprises age, sex, height, length, weight, handedness, average amount of daily physical activity, date of amputation, side of amputation, stump length, comorbidities,

Table 1. Outcome parameters.

Primary outcomes		
Brain neuroplasticity	MRI: brain connectivity & microstructure	[numeric]
Functional performance		
6-min walking test [43]	Distance covered in 6 minutes	[numeric]
Secondary outcomes		
Functional performance		
Slope walking test [40]	Time to complete test	[numeric]
Stair climbing and descending test [41]	Time to complete test	[numeric]
Dual-task L-test [42]	Time to complete test & accuracy of subtractions	[numeric]
L-test [42]	Time to complete test	[numeric]
6-min walking test [43]	Time to complete test	[numeric]
Biomechanical gait parameters	Lower limb joint angles and velocities & intra-limb continuous relative phases	[numeric]
Slope walking test [40]	Lower limb joint angles and velocities & intra-limb continuous relative phases	[numeric]
Stair climbing and descending test [41]	Lower limb joint angles and velocities & intra-limb continuous relative phases	[numeric]
6-min walking test [43]	Lower limb joint angles and velocities & intra-limb continuous relative phases	[numeric]
Scores		
Prosthetic Evaluation Questionnaire		[numeric, VAS, scale]
Quebec User Evaluation of Satisfaction with Assistive Technology		[numeric, scale]
NASA-Task-Load Index		[numeric, VAS]
L-test [42]		[numeric, VAS]
Dual-task L-test [42]		[numeric, VAS]
Level of comfort		[numeric, VAS]
Slope walking test [40]		[numeric, VAS]
Stair climbing and descending test [41]		[numeric, VAS]
Dual-task L-test [42]		[numeric, VAS]
L-test [42]		[numeric, VAS]
6-min walking test [43]		[numeric, VAS]
Level of fatigue		[numeric, VAS]
Slope walking test [40]		[numeric, VAS]
Stair climbing and descending test [41]		[numeric, VAS]
Dual-task L-test [42]		[numeric, VAS]
L-test [42]		[numeric, VAS]
6-min walking test [43]		[numeric, VAS]
Rate of perceived exertion		[numeric]
Slope walking test [40]		[numeric]
Stair climbing and descending test [41]		[numeric]
Dual-task L-test [42]		[numeric]
L-test [42]		[numeric]
6-min walking test [43]		[numeric]

MRI = Magnetic Resonance Imaging, VAS = Visual Analogue Scale

https://doi.org/10.1371/journal.pone.0299869.t001

use of medication, presence of phantom pains, history of trauma and the history of falls. During the follow-up measurements, we will again perform the anamnesis and extend this with questions on the rehabilitation process, if other prosthetic devices were tested, and the duration of prosthesis use throughout the day. Auxiliary subject information that will be gathered during the first day of data collection within the control group of able-bodied participants will comprise age, sex, height, length, weight, handedness and average daily physical activity.

Brain neuroplasticity. Neuroplasticity can be defined as a reorganisation of brain structure, function and connectivity within the central nervous system in response to intrinsic and extrinsic stimuli [28]. Based on our hypotheses, we are mainly interested in, but not limited to, the motor-related regions of the brain given the exploratory nature of this study [12]. The outcome parameters include connectivity and white and grey matter microstructure measures (e.g., characteristic path length, clustering coefficient, efficiency, neurite density index, fiber density, and fiber cross-section, fiber density cross-section).

Pre- and post-intervention MRI scans will be acquired supine on a 3-Tesla MRI unit using a 48-channel head coil. A 30-minute protocol will be followed, comprising scout images, 3D T1-weighted spin-echo images, diffusion-weighted imaging, resting state-fMRI, and 3D-QALAS. An anatomical 3D T1-weighted image and a multi-shell diffusion-weighted dataset will be acquired, as well as a resting-state fMRI acquisition and a 3D-QALAS acquisition. The diffusion dataset includes several b0 images, and for both the diffusion and resting state data, additional data using reversed-phase directions will be acquired. The 3D-QALAS acquisition allows for a simultaneous T1, T2 and proton density mapping, additional data using reversed-phase directions will be acquired, making it sensitive to microstructural changes in the brain [29, 30].

After data acquisition, the MRI data will be pre-processed, and the outcome parameters will be computed. FSL will be used to pre-process the diffusion-weighted imaging and resting state-fMRI data [31–33]. Pre-processing consists of denoising, distortion, eddy current and bias field correction, and motion correction with outlier replacement. Afterward, a MRtrix3 performs a fixed-based analysis in the white matter regions, while a NODDI analysis is done in the grey matter areas [34, 35]. To analyse the 3D-QALAS data, SyMRI will be used (SyntheticMR AB, Linköping, Sweden), after which grey matter, white matter and myelin maps are estimated from the relaxometry maps [36, 37]. Once the relaxometry and tissue maps are obtained, a voxel-based analysis will be performed using a modified version of the hMRI toolbox of SPM12 [38, 39], using MATLAB.

Functional performance & questionnaires. A 6-min walking test, dual-task L-test, L-test, slope walking test, and stairs climbing and descending test will indicate functional balance and dual-task performance [40–43]. Rating of perceived exertion [44], level of fatigue and comfort [45] and NASA-Task Load index (NASA-TLX) assessing perceived workload [46] will be assessed after each task.

Quality of life & prosthetic satisfaction. The prosthetic evaluation questionnaire will be used to assess the quality of life [22]. The Quebec User Evaluation of Satisfaction with Assistive Technology will be used to evaluate the prosthetic satisfaction and prosthetic associated services [23, 24].

Biomechanical gait parameters. Inertial measurements units (Awinda, Xsens Technologies B.V., Enschede, The Netherlands) will be capturing 3D-accelerations and angular velocities during the 6-min walking test, the slope walking test and the stairs climbing and descending test to evaluate the participants' gait pattern [47]. Inertial measurement units will be placed on the feet, lower legs, upper legs and pelvis according to the manufacture guidelines. The data of the inertial measurement units will be used to evaluate coordination patterns between hip, knee and ankle joints or segments based on continuous relative phase plots.

Biomechanical data will be analysed and purified in Matlab (The MathWorks Inc., Massachusetts, United States) following the methods described in Lathouwers et al (2023) [48].

Statistical analyses

Statistical analyses will be performed using R [49], MRtrix [50], and the hMRI toolbox [51]. Statistical methods for brain neuroplasticity and functional performance testing outcomes will include mixed linear or generalised linear modelling depending on the model assumptions being fulfilled. If those analyses cannot be conducted, assumptions will be checked to perform multivariate or univariate analyses. If the assumptions for those types of analyses are also not fulfilled, non-parametric equivalents will be applied. The data will be adjusted for confounding variables like age, sex, handedness, amount of daily prosthetic use and the average amount of daily physical activity. The biomechanical gait parameters will be compared within and between groups using statistical parametric or non-parametric mapping. The statistical significance level will be set at 5% for all analyses.

Data storage and management

As personal and sensitive data of human participants will be collected, pseudonymisation of the data will occur as soon as possible upon data acquisition. The file, which establishes the link between the pseudonymised identities and the participant's identification, will be password-protected.

Raw data from the anamnesis, functional performance tests and questionnaires will be collected via an electronic case report form using Redcap (projectredcap.org). Data collected in Redcap is automatically stored on the external server of the Ethical Committee of the UZ Brussel. Upon completion of the data collection, the data collected via Redcap will be downloaded from the software application and used for data processing and analyses. Both the raw and cleaned data will be stored on the research's group network attached storage (NAS). Raw biomechanical and MRI data will be stored on the research's group network attached storage (NAS). After data processing, the cleaned data will be stored on the NAS. The NAS is system-encrypted, back-upped, has up-to-date antivirus and is only accessible by authorised personnel via two-factor authentication. Manual files will be stored in locked filing cabinets. All pseudonymized data will be stored for up to 10 years, as recommended by the Vrije Universiteit Brussel.

Data in the present study will be managed confidentially and conform to the General Data Protection Regulation (GDPR) of 27 April 2016. Participating in this study means that the participant agrees that the investigators gather data of the participant that will be used to conduct the investigation and eventually will result in publications in scientific journals and presentations at conferences. By signing the informed consent, participants also provide their agreement that encoded data may be shared with other researchers beyond the scope of the current study. The participant will always have the right to ask the investigators which data he/she has gathered on them and for what this data is used in light of the investigation. The participant retains the right to look into this data and to ask for corrections on the occasion this data contains errors. The participant also retains the right to stop his/her participation in the study at any moment.

In order to control the quality of the present study, the medical file of the participants may be consulted. If so, this will be done by qualified personnel bound to professional secrecy, e.g. representatives of the ethical committee or an external auditing bureau. This consultation can only occur under strict conditions, under the investigator's responsibility and supervision. The

encrypted data can also be passed through the Belgium government, other regulatory authorities, or the ethical committee.

Ethics and dissemination

The study is approved by the medical ethics commission of VUB and UZ Brussel (BUN 1432023000077), and is registered via Clinical.trials.gov (NCT05818410). Written informed consent will be obtained from all participants.

The authors of the present protocol proposal declare no financial or other conflicts of interest.

Trial results will be communicated to the general public through the publication of disseminated manuscripts published in scientific journals, and through conference presentations/ posters. Authorship of these papers and presentations will only be granted to researchers that performed a substantial contribution to the scientific article [52]. Given the nature of this paper (i.e. protocol paper), data has yet to be gathered. After data collection and analysis, the statistical code and dataset will be freely available in a to-be-determined online repository for lasting access possibility.

Discussion & conclusion

This study will examine differences in brain neuroplasticity through MRI between individuals wearing a new passive ankle prosthesis with an articulated ankle joint and a standard passive ankle prosthesis. The secondary aim is to investigate walking performance and quality of life-related to the type of prosthesis, and the final aim is to determine if the type of prosthesis changes the movement pattern during walking.

This novelty of the study stems from it being the first to unravel possible differences in neuroplasticity in relation to the type of prosthesis in patients with a lower-extremity amputation. It could provide valuable insights into how the brain adapts to various prosthetic types, complementing the existing literature on neuroplasticity after amputation [12]. Depending on the findings of this study, these results may have a societal impact and improve the quality of life for individuals with lower limb amputation.

Furthermore, this study will generate biopsychosocial findings on the therapeutic health benefits of prostheses on individuals with an amputation (i.e. functional performance and quality of life) through both subjective and objective parameters. The study will, therefore, take a first step in filling the literature gap regarding medium- to longer-term prosthetic effects on the individual wearing the prosthesis [15]. The findings from this study may serve as a stepping stone for future research, fostering a deeper understanding of the overall impact of prosthetic interventions. Additionally, they have the potential to inform future advancements in prosthetic design and rehabilitation strategies, aiming to improve the quality of life of patients with an amputation and decrease the associated mortality risk.

Supporting information

S1 Table. Trial registration data.
(DOCX)

S1 Protocol. Original protocol.
(PDF)

S1 Checklist. SPIRIT 2013 checklist: Recommended items to address in a clinical trial protocol and related documents*.
(DOC)

Acknowledgments

Author Contributions

References

1. Manz S, Valette R, Damonte F, Avanci Gaudio L, Gonzalez-Vargas J, Sartori M, et al. A review of user needs to drive the development of lower limb prostheses. J Neuroeng Rehabil. 2022; 19(1):119. Epub 20221105. https://doi.org/10.1186/s12984-022-01097-1 PMID: 36335345.

2. Grzebień A, Chabowski M, Malinowski M, Uchmanowicz I, Milan M, Janczak D. Analysis of selected factors determining quality of life in patients after lower limb amputation- a review article. Pol Przegl Chir. 2017; 89(2):57–61. https://doi.org/10.5604/01.3001.0009.8980 PMID: 28537564.

3. Farrokhi S, Mazzone B, Yoder A, Grant K, Wyatt M. A Narrative Review of the Prevalence and Risk Factors Associated With Development of Knee Osteoarthritis After Traumatic Unilateral Lower Limb Amputation. Mil Med. 2016; 181(S4):38–44. https://doi.org/10.7205/MILMED-D-15-00510 PMID: 27849460.

4. Gailey R, Allen K, Castles J, Kucharik J, Roeder M. Review of secondary physical conditions associated with lower-limb amputation and long-term prosthesis use. J Rehabil Res Dev. 2008; 45(1):15–29. https://doi.org/10.1682/jrrd.2006.11.0147 PMID: 18566923.

5. Highsmith MJ, Goff LM, Lewandowski AL, Farrokhi S, Hendershot BD, Hill OT, et al. Low back pain in persons with lower extremity amputation: a systematic review of the literature. Spine J. 2019; 19 (3):552–63. Epub 20180824. https://doi.org/10.1016/j.spinee.2018.08.011 PMID: 30149083.

6. Sivapuratharasu B, Bull AMJ, McGregor AH. Understanding Low Back Pain in Traumatic Lower Limb Amputees: A Systematic Review. Arch Rehabil Res Clin Transl. 2019; 1(1–2):100007. Epub 20190625. https://doi.org/10.1016/j.arrct.2019.100007 PMID: 33543047.

7. Steinberg N, Gottlieb A, Siev-Ner I, Plotnik M. Fall incidence and associated risk factors among people with a lower limb amputation during various stages of recovery—a systematic review. Disabil Rehabil. 2019; 41(15):1778–87. Epub 2018/03/16. https://doi.org/10.1080/09638288.2018.1449258 PMID: 29540083.

8. Chihuri ST, Youdan GA Jr, Wong CK. Quantifying the risk of falls and injuries for amputees beyond annual fall rates—A longitudinal cohort analysis based on person-step exposure over time. Preventive Medicine Reports. 2021; 24:101626. https://doi.org/10.1016/j.pmedr.2021.101626 PMID: 34976679

9. Hartholt KA, van Beeck EF, Polinder S, van der Velde N, van Lieshout EM, Panneman MJ, et al. Societal consequences of falls in the older population: injuries, healthcare costs, and long-term reduced quality of life. J Trauma. 2011; 71(3):748–53. https://doi.org/10.1097/TA.0b013e3181f6f5e5 PMID: 21045738.

10. Mundell B, Maradit Kremers H, Visscher S, Hoppe K, Kaufman K. Direct medical costs of accidental falls for adults with transfemoral amputations. Prosthetics and Orthotics International. 2017; 41(6):564–70. https://doi.org/10.1177/0309364617704804 PMID: 28641476

11. Rodrigues FB, Andrade AO, Vieira MF. Effects of inclined surfaces on gait variability and stability in unilateral lower limb amputees. Med Biol Eng Comput. 2019; 57(11):2337–46. Epub 2019/09/12. https://doi.org/10.1007/s11517-019-02042-6 PMID: 31506856.

12. Molina-Rueda F, Navarro-Fernández C, Cuesta-Gómez A, Alguacil-Diego IM, Molero-Sánchez A, Carratalá-Tejada M. Neuroplasticity Modifications Following a Lower-Limb Amputation: A Systematic Review. Pm r. 2019; 11(12):1326–34. Epub 2019/04/17. https://doi.org/10.1002/pmrj.12167 PMID: 30989836.

13. Wittenberg E, Thompson J, Nam CS, Franz JR. Neuroimaging of Human Balance Control: A Systematic Review. Frontiers in Human Neuroscience. 2017; 11. https://doi.org/10.3389/fnhum.2017.00170 PMID: 28443007

14. Windrich M, Grimmer M, Christ O, Rinderknecht S, Beckerle P. Active lower limb prosthetics: a systematic review of design issues and solutions. BioMedical Engineering OnLine. 2016; 15(3):140. https://doi.org/10.1186/s12938-016-0284-9 PMID: 28105948

15. Russell Esposito E, Aldridge Whitehead JM, Wilken JM. Step-to-step transition work during level and inclined walking using passive and powered ankle-foot prostheses. Prosthet Orthot Int. 2016; 40 (3):311–9. Epub 2015/01/30. https://doi.org/10.1177/0309364614564021 PMID: 25628378.

16. Voloshina AS, Collins SH. Chapter 23—Lower limb active prosthetic systems—overview. In: Rosen J, Ferguson PW, editors. Wearable Robotics: Academic Press; 2020. p. 469–86.

17. Lathouwers E, Díaz MA, Maricot A, Tassignon B, Cherelle C, Cherelle P, et al. Therapeutic benefits of lower limb prostheses: a systematic review. Journal of NeuroEngineering and Rehabilitation. 2023; 20 (1):4. https://doi.org/10.1186/s12984-023-01128-5 PMID: 36639655

18. De Pauw K, Cherelle P, Tassignon B, Van Cutsem J, Roelands B, Marulanda FG, et al. Cognitive performance and brain dynamics during walking with a novel bionic foot: A pilot study. PLOS ONE. 2019; 14(4):e0214711. https://doi.org/10.1371/journal.pone.0214711 PMID: 30943265

19. Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin JA, et al. SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. BMJ: British Medical Journal. 2013; 346:e7586. https://doi.org/10.1136/bmj.e7586 PMID: 23303884

20. Howard CL, Wallace C, Perry B, Stokic DS. Comparison of mobility and user satisfaction between a microprocessor knee and a standard prosthetic knee: a summary of seven single-subject trials. Int J Rehabil Res. 2018; 41(1):63–73. Epub 2018/01/03. https://doi.org/10.1097/MRR.0000000000000267 PMID: 29293160.

21. WMA. Declaration of Helsinki: ethical principles for medical research involving human subjects. J Am Coll Dent. 2014; 81(3):14–8. Epub 2015/05/09. PMID: 25951678.

22. Boone DA, Coleman KL. Use of the Prosthesis Evaluation Questionnaire (PEQ). JPO: Journal of Prosthetics and Orthotics. 2006; 18(6).

23. Demers L, Weiss-Lambrou R, Ska B. The Quebec User Evaluation of Satisfaction with Assistive Technology (QUEST 2.0): An overview and recent progress. Technology and Disability. 2002; 14:101–5. https://doi.org/10.3233/TAD-2002-14304

24. Aledda S, Galeoto G, Fabbrini G, Lucibello L, Tofani M, Conte A, et al. A systematic review of the psychometric properties of Quebec user evaluation of satisfaction with assistive technology (QUEST). Disability and Rehabilitation: Assistive Technology. 2023:1–8. https://doi.org/10.1080/17483107.2022.2161648 PMID: 36645802

25. Rogge A-K, Röder B, Zech A, Hötting K. Exercise-induced neuroplasticity: Balance training increases cortical thickness in visual and vestibular cortical regions. NeuroImage. 2018; 179:471–9. https://doi.org/10.1016/j.neuroimage.2018.06.065 PMID: 29959048

26. Rogge AK, Röder B, Zech A, Nagel V, Hollander K, Braumann KM, et al. Balance training improves memory and spatial cognition in healthy adults. Sci Rep. 2017; 7(1):5661. Epub 20170718. https://doi.org/10.1038/s41598-017-06071-9 PMID: 28720898.

27. Mahon CE, Hendershot BD. Biomechanical accommodation to walking with an ankle–foot prosthesis: An exploratory analysis of novice users with transtibial limb loss within the first year of ambulation. Prosthetics and Orthotics International. 2022: https://doi.org/10.1097/PXR.0000000000000124 PMID: 35333820

28. Puderbaugh M, Emmady PD. Neuroplasticity. StatPearls. Treasure Island (FL): StatPearls Publishing Copyright © 2023, StatPearls Publishing LLC.; 2023.

29. Fujita S, Hagiwara A, Hori M, Warntjes M, Kamagata K, Fukunaga I, et al. Three-dimensional high-resolution simultaneous quantitative mapping of the whole brain with 3D-QALAS: An accuracy and repeatability study. Magn Reson Imaging. 2019; 63:235–43. Epub 20190821. https://doi.org/10.1016/j.mri.2019.08.031 PMID: 31445118.

30. Kvernby S, Warntjes MJ, Haraldsson H, Carlhäll CJ, Engvall J, Ebbers T. Simultaneous three-dimensional myocardial T1 and T2 mapping in one breath hold with 3D-QALAS. J Cardiovasc Magn Reson. 2014; 16(1):102. Epub 20141220. https://doi.org/10.1186/s12968-014-0102-0 PMID: 25526880.

31. Jenkinson M, Beckmann CF, Behrens TE, Woolrich MW, Smith SM. FSL. Neuroimage. 2012; 62 (2):782–90. Epub 20110916. https://doi.org/10.1016/j.neuroimage.2011.09.015 PMID: 21979382.

32. Smith SM, Jenkinson M, Woolrich MW, Beckmann CF, Behrens TE, Johansen-Berg H, et al. Advances in functional and structural MR image analysis and implementation as FSL. Neuroimage. 2004; 23 Suppl 1:S208–19. https://doi.org/10.1016/j.neuroimage.2004.07.051 PMID: 15501092.

33. Woolrich MW, Jbabdi S, Patenaude B, Chappell M, Makni S, Behrens T, et al. Bayesian analysis of neuroimaging data in FSL. Neuroimage. 2009; 45(1 Suppl):S173–86. Epub 20081113. https://doi.org/10.1016/j.neuroimage.2008.10.055 PMID: 19059349.

34. MRtrix. Fibre density and cross-section—Single-tissue CSD—MRtrix 3.0 documentation [cited 2022]. https://mrtrix.readthedocs.io/en/dev/fixel_based_analysis/st_fibre_density_cross-section.html.

35. Zhang H, Schneider T, Wheeler-Kingshott CA, Alexander DC. NODDI: practical in vivo neurite orientation dispersion and density imaging of the human brain. Neuroimage. 2012; 61(4):1000–16. Epub 20120330. https://doi.org/10.1016/j.neuroimage.2012.03.072 PMID: 22484410.

36. Hagiwara A, Warntjes M, Hori M, Andica C, Nakazawa M, Kumamaru KK, et al. SyMRI of the Brain: Rapid Quantification of Relaxation Rates and Proton Density, With Synthetic MRI, Automatic Brain Segmentation, and Myelin Measurement. Invest Radiol. 2017; 52(10):647–57. https://doi.org/10.1097/RLI.0000000000000365 PMID: 28257339.

37. West J, Warntjes JB, Lundberg P. Novel whole brain segmentation and volume estimation using quantitative MRI. Eur Radiol. 2012; 22(5):998–1007. Epub 20111124. https://doi.org/10.1007/s00330-011-2336-7 PMID: 22113264.

38. Friston KJ, Glaser DE, Henson RN, Kiebel S, Phillips C, Ashburner J. Classical and Bayesian inference in neuroimaging: applications. Neuroimage. 2002; 16(2):484–512. https://doi.org/10.1006/nimg.2002.1091 PMID: 12030833.

39. Tabelow K, Balteau E, Ashburner J, Callaghan MF, Draganski B, Helms G, et al. hMRI—A toolbox for quantitative MRI in neuroscience and clinical research. Neuroimage. 2019; 194:191–210. Epub 20190121. https://doi.org/10.1016/j.neuroimage.2019.01.029 PMID: 30677501.

40. Agrawal V, Gailey RS, Gaunaurd IA, O'Toole C, Finnieston A, Tolchin R. Comparison of four different categories of prosthetic feet during ramp ambulation in unilateral transtibial amputees. Prosthetics and Orthotics International. 2015; 39(5):380–9. https://doi.org/10.1177/0309364614536762 PMID: 24925671.

41. Schmalz T, Blumentritt S, Marx B. Biomechanical analysis of stair ambulation in lower limb amputees. Gait & Posture. 2007; 25(2):267–78. https://doi.org/10.1016/j.gaitpost.2006.04.008 PMID: 16725325

42. Hunter SW, Frengopoulos C, Holmes J, Viana R, Payne MW. Determining Reliability of a Dual-Task Functional Mobility Protocol for Individuals With Lower Extremity Amputation. Arch Phys Med Rehabil. 2018; 99(4):707–12. Epub 2018/01/11. https://doi.org/10.1016/j.apmr.2017.12.008 PMID: 29317224.

43. Cox PD, Frengopoulos CA, Hunter SW, Sealy CM, Deathe AB, Payne MWC. Impact of Course Configuration on 6-Minute Walk Test Performance of People with Lower Extremity Amputations. Physiother Can. 2017; 69(3):197–203. https://doi.org/10.3138/ptc.2016-24 PMID: 30275635.

44. Borg GA. Psychophysical bases of perceived exertion. Medicine & science in sports & exercise. 1982.

45. Lee KA, Hicks G, Nino-Murcia G. Validity and reliability of a scale to assess fatigue. Psychiatry Res. 1991; 36(3):291–8. Epub 1991/03/01. https://doi.org/10.1016/0165-1781(91)90027-m PMID: 2062970.

46. Hart SG, Staveland LE. Development of NASA-TLX (Task Load Index): Results of Empirical and Theoretical Research. In: Hancock PA, Meshkati N, editors. Advances in Psychology. 52: North-Holland; 1988. p. 139–83.

47. Cho YS, Jang SH, Cho JS, Kim MJ, Lee HD, Lee SY, et al. Evaluation of Validity and Reliability of Inertial Measurement Unit-Based Gait Analysis Systems. Ann Rehabil Med. 2018; 42(6):872–83. Epub 2019/01/08. https://doi.org/10.5535/arm.2018.42.6.872 PMID: 30613081.

48. Lathouwers E, Baeyens JP, Tassignon B, Gomez F, Cherelle P, Meeusen R, et al. Continuous relative phases of walking with an articulated passive ankle-foot prosthesis in individuals with a unilateral

transfemoral and transtibial amputation: an explorative case-control study. Biomed Eng Online. 2023; 22(1):14. Epub 20230215. https://doi.org/10.1186/s12938-023-01074-2 PMID: 36793091.

49. R Development Core Team. R: A Language and Environment for Statistical Computing. R Foundation for Statistical Computing. 2019.

50. Tournier JD, Smith R, Raffelt D, Tabbara R, Dhollander T, Pietsch M, et al. MRtrix3: A fast, flexible and open software framework for medical image processing and visualisation. NeuroImage. 2019; 202:116137. https://doi.org/10.1016/j.neuroimage.2019.116137 PMID: 31473352

51. Tabelow K, Balteau E, Ashburner J, Callaghan MF, Draganski B, Helms G, et al. hMRI–A toolbox for quantitative MRI in neuroscience and clinical research. NeuroImage. 2019; 194:191–210. https://doi.org/10.1016/j.neuroimage.2019.01.029 PMID: 30677501

52. Kassirer JP, Angell M. On Authorship and Acknowledgments. New England Journal of Medicine. 1991; 325(21):1510–2. https://doi.org/10.1056/NEJM199111213252112 PMID: 1944431