MEDIZINISCHE UNIVERSITÄT WIEN

Clinical Investigation Plan (Klinischer Prüfplan), Version 1.2

Central programming in patients with a bionic hand after traumatic brachial plexus injury

"Zentrale Programmierung von PatientInnen mit einer bionischen Rekonstruktion nach einer Plexusparese"

Sponsor

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Abstract

Traumatic brachial plexus lesions may lead to permanent impairment of hand function despite brachial plexus surgery. In selected cases the affected forearm can be amputated and replaced by a bionic hand. It is unclear how cortical activation patterns change after the injury and after acquisition of the hand prosthesis considering the complex changes in sensory and motor feedback.

The aim of the study is to measure cortical activity with fMRI during actual and imagery movements with the affected and healthy arm in a group of patients after traumatic brachial plexus injury and a group in whom this was followed by replacement with a bionic hand.

In this prospective study three groups of patients will participate: 1) 3 adult patients with a traumatic brachial plexus lesion eligible for a bionic arm but prior to its acquisition, 2) 3 patients with a traumatic brachial plexus lesion who have acquired the bionic arm already, and 3) 10 healthy subjects. We will measure cortical activity using fMRI BOLD tasks of closing the hand and motor imagery of this movement. Cortical activity will be compared between the three groups. Additionally, regional gray matter volume, resting-state, and DTI networks will be studied. Written informed consent will be provided prior to the investigation. The complete examination has a duration of approximately 45 minutes.

Introduction

In this study we want to investigate what changes take place in the brain after a traumatic brachial plexus lesion followed by acquiring a bionic hand. These patients have acquired a global brachial plexus injury including avulsions of the lower nerve roots (C8-Th1), which are responsible for hand function. They have a poor hand function despite brachial plexus surgery. After an extensive training program these patients acquire a myoelectric hand prosthesis (Sensor hand speed (Otto Bock HealthCare Deutschland, GmbH, Germany) or similar) and their affected hand is amputated. The acquired bionic hand is surface EMG driven by the remaining arm muscles after nerve and muscle transfer, if necessary. (Aszmann, et al., 2015; Sturma et al, 2018) Thus, the patients have to learn how to control the bionic hand with new motor and sensory feedback signals. It is unclear what changes occur in the brain to succeed at this.

Functional MRI (fMRI) can identify cortical plasticity in humans. (Anastakis et al., 2005) Additional motor imagery tasks allow us to assess the changes in cortical areas involved in motor planning. (Decety and Grezes, 1999) We know that motor cortical areas expand at the onset of learning a new motor skill in healthy subjects, but also in patients following upper extremity injury and reconstruction. (Anastakis et al., 2005) These areas decrease again when a skill is being mastered. (Anastakis et al., 2005) In amputees a higher contralateral cortical activation was found during imagined phantom hand movements compared to healthy subjects. (Lotze et al., 2001) It has been suggested that this is due to an increased central effort required for action planning. (Hotz-Boendermaker et al., 2008) However, motor imagery ability of the affected and unaffected limbs in patients with complete traumatic brachial plexus palsy has been shown to decrease, possibly due to long-term disuse. (Date et al., 2019) And in adults with an obstetric brachial plexus lesion cortical activation is increased only for movement planning but not actual movement. (Anguelova et al., 2017) Cortical changes have also been found when using the healthy arm in these patients. (Anguelova et al., 2017)

Thus, the aim of this study is to elucidate with fMRI what changes occur in cortical activity in patients with a traumatic brachial plexus lesion followed by forearm amputation and acquisition of a bionic hand. Understanding what cortical changes occur, may help us in the future to acquire a better patient selection for this intervention and possibly improve rehabilitation schemes.

Research questions

1) Does the cortical activation increase in the contralateral hemisphere during movement of the corresponding affected arm after traumatic plexus lesion compared to healthy subjects?

2) Are different cortical areas activated in the contralateral hemisphere during movement of the affected arm after traumatic plexus lesion than those in healthy subjects or does the expected area of activation expand?

3) Does cortical activity increase or expand in the ipsilateral hemisphere (responsible for the healthy arm) during movement of the affected arm after traumatic plexus lesion?

4) Does cortical activity increase or expand in both hemispheres during movement of the healthy arm after traumatic plexus lesion?

All of the above questions will be addressed for two groups of patients: 1. patients who are eligible for bionic reconstruction but have not acquired it yet, and 2. patients with a bionic arm.

Hypothesis

Cortical activity increases and the area expands which is responsible for performing and planning a motor task in patients after traumatic brachial plexus lesion prior as well after bionic hand acquisition compared to healthy control subjects for both the affected and unaffected side.

Design

a) Selection of experimental subjects

A group of 3 adult patients who acquired a bionic hand at the Medical University of Vienna after a traumatic brachial plexus lesion, and a group of 3 patients eligible for the bionic hand prior to a possible amputation will be included. The number of patients included is based on the rarity of the procedure and thus the very limited number of eligible study participants. Ten control subjects will be included for comparison. An inclusion criterion for all participants is an age above 18, and that they understand German or English. Brachial plexus surgery is not an exclusion criterium for patients. Patients with a bionic hand are selected who are able to open and close the hand prosthesis. The standard contraindications for MRI will be checked for according to hospital protocol (ferromagnetic devices such as clips, claustrophobia, etc.) and, if necessary, patients will be excluded from participation.

b) Procedure

Cortical activation is measured with a Philips Achieva 3 Tesla MRI scanner at the University Department of Radiology and Nuclear Medicine of Vienna General Hospital. The MRI protocol will include the following sequences: T1-weighted anatomical scan, T2-weighted task related scans, resting-state, and DTI-sequence.

Participants are requested to isometrically close their hand at the rate of 1Hz. This means to repeatedly squeeze their closed fist tight without an observed movement, thus avoiding MRI movement artifacts. This movement is selected based on a surface EMG signal to noise ratio higher than 3 in the patients with a bionic hand from a pilot study prior to this investigation. The arms are positioned in a straight position next to the body with the hand palm facing the body. Participants are instructed to lie still during the experiment. For the motor imagery task, participants are requested to imagine rhythmically (1Hz) performing the same movement. The tasks (execution and imagery) are performed by all participants (all three groups) with both arms separately.

Task based fMRI will be applied using a block-design-paradigm to assess cortical activation patterns. Task instructions are represented by a visual and an audio cue. The visual cue is an image of a hand, either left or right corresponding to the task, which is presented on a computer screen using SensaVue and projected onto a mirror above the eyes of the subject. The audio cue indicates to either execute or imagine isometrically closing the hand and states which side to use (left or right). The audio instructions are given by the investigator through the MRI intercom before the start of the task. A crossed hand indicates rest (baseline). A thirty second baseline block is presented followed by a thirty second task block, comprising one cycle. A cycle is repeated five times during a total of five minutes. A total of four conditions is used in the same order for all participants: 1. execution left arm, 2. execution right arm, 3. imigary left arm, 4. imigary right arm. Subjects are given a break to rest (not scanning) between the four conditions, until they indicate they are ready to continue, to minimize the effects of (muscle) fatigue.

A 10 minute fMRI resting-state sequence will be acquired to assess ongoing functional communication between brain regions during rest. For this sequence participants are instructed to think of nothing in specific while keeping the eyes closed. An 8 minute DTI-sequence will be acquired to assess the structural/anatomical brain connectivity; thus, no specific task is requested form participants.

An electromyography (EMG) training session prior to MRI scanning is used to assure the tasks are executed as requested. EMG is measured with electrodes placed over the muscle belly of the flexor digitorum superficialis and profundus in control subjects, the healthy arm in all patients, and the affected arm in patients who have not undergone amputation and prosthetic fitting yet. (Hermens et al., 1999) For the patients who have acquired a bionic hand already, the position of the electrode used for "hand close" within their prosthetic fitting is used. During MRI measurement the bionic hand is placed outside the MRI scanner as it is not MRI compatible but could be observed by the patients during the EMG training session. During the training session participants observe their EMG activity during the tasks on a screen. They are instructed to aim for activity in the agonist and reduce activity in the antagonist as much as possible during execution and not to activate both agonist and antagonist during imagery squeezing of the fist. Responses are acquired using a band pass filter of 20 Hz–2 kHz and recorded over a minimum of 100 s using. For recording the surface EMG either the MyoBoy in combination with the PAULA Software (both from Ottobock Health Care GmbH, Duderstatt, Germany) or the TeleMyo 2400T G2 System with myoMUSCLE Master software (both from Noraxon, Scottsdale, US) will be used. Both systems are CE-certified medical products.

b) Analysis

Cortical activity is compared between patients and control subjects as follows.

fMRI data will be preprocessed with the SPM12 software package (Wellcome Department of Cognitive Neurology, Institute of Neurology, University College London, UK) in the MATLAB R2017a programming environment (MathWorks, Inc.; Natick,MA, USA). The following processing steps are applied: motion correction (Jenkinson et al., 2002), removal of non-brain tissue, (Smith, 2002) spatial smoothing using a Gaussian kernel of 8 mm full width at half maximum, grand-mean intensity normalization of the entire 4D dataset by a single multiplicative factor and high-pass temporal filtering (Gaussian-weighted least-squares straight line fitting, with a 128 s cut-off). To register fMRI scans to standard space, functional scans of an individual are registered to the corresponding T2-weighted images, which are registered to the T1-weighted images, followed by registration to MNI-152 standard space (T1 standard brain averaged over 152 subjects; Montreal Neurological Institute, Montreal, QC, Canada) images (Jenkinson and Smith, 2001; Jenkinson et al., 2002). Preprocessed MRI data of patients with an affected left arm are mirrored with respect to the midsagittal plane (Ward and Frackowiak, 2003). In this way the hemisphere corresponding with the affected hand is on the same (left) side for all patients and the right hemisphere corresponds with the unaffected hand. This is also done for the healthy subjects: the hemisphere responsible

for the non-dominant hand will, if necessary, be mirrored to be on the left side. Patients will be asked for how many days of the week and how many hours a day on avarage they have used the prosthesis in the past two weeks, as a possible correction factor (independent variable) for the amount of motor cortex activation. Additionally, resting-state networks, DTI data and regional gray matter volume will be compared between patients and healthy subjects.

EMG activity before MRI scanning is compared for the patient and control groups, and for each muscle and task separately. To exclude learning effects the first 50 s of the EMG signal for each of the four conditions (motor imagery/movement, right/left hand) are excluded from analysis. The EMG signal is then rectified and the sum of values between 50 and 100 s of the recording is calculated. The non-parametric dependent samples Wilcoxon's test is used in IBM SPSS Statistics 25 with a significance threshold of 0.05.

Risk – benefit assessment

The risk for study participation is negligible. If the experienced inconvenience turns out to be unexpectedly greater than estimated by the subject beforehand then participation in the investigation is stopped immediately.

As no medical treatment is delivered, the benefits for the participants will be relatively little. For some of the amputees or participants with severe nerve injuries, it might be interesting to better understand how they cortically adapted to the situation. Additionally, participants will support basic research that might in the future have applications in the field of human-machine interfacing in healthy people and individuals with injuries and impairments. It is, however, unlikely that the cohort of participants supporting us within this study will ever directly benefit from the experiments.

In summary, we do neither expect any great benefits nor any risks for the participants. As this is basic research, we do, however, hope to be able to use the findings to develop better rehabilitation technology in the future. This might include better interfaces for prosthetic control as well as better tools for the rehabilitation after nerve injuries.

As we cannot guarantee that the participants will benefit from any of the possible future applications, we plan to compensate their time spend within the study with 10€/hour and reimburse their travel expenses.

Experimental subjects: informed consent procedure

Written informed consent will be required before performing the investigation. Not participating in the study or withdrawal from the study will not have any negative effects for the participants and will not affect the medical treatment of patients.

Discontinuation/withdrawal of participants from study

Each participant has the right to withdraw study at any time without needing to give a reason for withdrawal. In addition, the investigator may discontinue a participant from the study at any time if the investigator considers it necessary for any reason including:

- Ineligibility
- Significant protocol deviation
- Significant non-compliance with study requirements
- An adverse event which makes further participation not possible
- Consent withdrawn

The reason for withdrawal will be recorded. If the participant is withdrawn due to an adverse event, the investigator will arrange for follow-up visits or telephone calls until the adverse event has resolved or stabilised. Only after participant approval, data already collected before withdrawal from the study will be included in the analysis.

Duration and scale

Participants will be contacted and scanned (training session prior to scanning included) from September 2020 onwards (pending ethical approval).
Eligible participants will receive an information letter with an attached informed consent form and an enclosed return envelope.
Expected time for scanning is 45 minutes. Including the time for EMG training and instructions before scanning, the full duration of one experiment is 1.5 to 2 hours.

Procedure for handling study results

Research data will be processed under a number for each patient. The gathered MRI scans will be saved and managed corresponding to that number in a file. The data are accessible exclusively to the involved investigators:
- Dr. ir. Galia V. Anguelova, Haaglanden Medical Centre, The Hague, The Netherlands
- Dr. Agnes Sturma, Medical University of Vienna
- Anna Bösendorfer, Medical University of Vienna
- Mehmet Salih Yildirim, Medical University of Vienna
- Victor Schmidbauer, Medical University of Vienna
- Dr. Gregor Kasprian, Medical University of Vienna
- Prof. Dr. Oskar Aszmann, Medical University of Vienna

We will not share any study results with researchers outside the EU. Currently, there are no plans for making any data sets fully publicly available via any open data platform. If any data sets will be made publicly available in the future, this will happen after consultation of the Medical University of Vienna's data clearing committee. (https://www.meduniwien.ac.at/web/ueber-uns/organisation/gremien/daten-clearingstelle/).

Should incidental findings of clinical relevance occur, we will follow the recommendations from "Managing Incidental Findings in Human Subjects Research: Analysis and Recommendations" by Wolf S et al.

Compensation

Traveling expenses and time spent on the experiment will be compensated for with 10€/hours.

Safety reporting and insurance

Any adverse events happening during the experiments will be recorded and reported to the Ethical Committee of the Medical University of Vienna. An insurance covers injuries or impairments resulting from study participation. Details in regard to the insurance can also be found in the participant information sheet.

Agreements on publication

Publications will take place in peer reviewed journals. No obligations by contract have been made. No commercial interests are at issue; manufacturers of prosthetic hands are not involved in data collection, analysis or interpretation.

Funding statement

Haaglanden Medical Centre (the Hague, the Netherlands) is funding the on site participation of dr.ir. G.V. Anguelova for the duration of four months as part of her neurology training. She is joining the Medical University as a Visiting Researcher.

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