Evaluation of the effects of adding vibrotactile feedback to myoelectric prosthesis users on performance and visual attention in a dual-task paradigm

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Abstract

Objective: To evaluate the effects of adding vibrotactile feedback to myoelectric prosthesis users on the performance time and visual attention in a dual-task paradigm.

Design: A repeated-measures design with a counterbalanced order of two conditions.

Setting: Laboratory setting.

Subjects: Transradial amputees using a myoelectric prosthesis with normal or corrected eyesight (N = 12, median age = 65 ± 13 years). Exclusion criteria were orthopedic or neurologic problems.

Interventions: Subjects performed grasping tasks with their prosthesis, while controlling a virtual car on a road with their intact hand. The dual task was performed twice: with and without vibrotactile feedback.

Main measures: Performance time of each of the grasping tasks and gaze behavior, measured by the number of times the subjects shifted their gaze toward their hand, the relative time they applied their attention to the screen, and percentage of error in the secondary task.

Results: The mean performance time was significantly shorter (P = 0.024) when using vibrotactile feedback (93.2 ± 9.6 seconds) compared with the performance time measured when vibrotactile feedback was not available (107.8 ± 20.3 seconds). No significant differences were found between the two conditions in the number of times the subjects shifted their gaze toward their hand, in the time the subjects applied their attention to the screen, and in the time the virtual car was off-road, as a percentage of the total game time (51.4 ± 15.7 and 50.2 ± 19.5, respectively).

Conclusion: Adding vibrotactile feedback improved performance time during grasping in a dual-task paradigm. Prosthesis users may use vibrotactile feedback to perform better during daily tasks, when multiple cognitive demands are present.

Keywords

Cognitive load, transradial amputation, motor control

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Introduction

One of the main challenges during rehabilitation following limb loss is the efficient use of a prosthetic hand in daily life. Transradial amputees may use either a body-powered or an electric-powered prosthesis. The latter can be controlled by a linear actuator, a pressure transducer, or by electrical signals generated by intact muscles and translated by electric motors into motion in the prosthesis. A prosthesis controlled by the use of electric signals from the muscles is called a myoelectric prosthesis. However, myoelectric prostheses inherently lack tactile feedback; therefore, the users of these devices have to rely on their visual feedback. As the amputee is required to use his or her visual feedback resources, grasping and manipulating objects in a successful manner may prove a challenging task. As a result, prosthesis users tend to focus their gaze on the prosthesis, thus elevating the cognitive load during motor performance.

One common method to provide tactile feedback to prostheses is vibrotactile feedback (VTF). Force sensors placed on the prosthetic fingers sense a grasped object, in turn triggering vibration through small vibration actuators, placed on the skin on the intact part of the limb. Despite the common use of VTF in published literature, the possible effects of adding VTF on the performance and gaze behavior in prosthesis users were not thoroughly investigated. Since myoelectric prostheses lack sensation and therefore require significant visual attention, we hypothesized that adding VTF to prostheses may improve performance during grasp and manipulation tasks and reduce the visual attention required to monitor the actions of the prosthesis, thus reducing the cognitive load of the user.

When grasping is performed as a single task, the user will usually allocate his or her attention to the prosthesis. However, since daily tasks may be performed in a dual-task paradigm, for example, holding a coffee cup while reading a newspaper or folding clothes while watching TV, they pose a cognitive challenge to the prosthesis user. Since the biological tactile feedback is not available to prosthesis users, there is an uncertainty during the process of grasping, resulting in increased cognitive workload. In a study examining the cognitive demands underlying the process of grasping objects, subjects were provided with tactile feedback during grasping, which was found to significantly improve the control of grip force. The cognitive load of using a myoelectric prosthesis appears to negatively affect a successful prosthetic rehabilitation, as prosthesis users report that the high cognitive demands affects their decision to reject using their prosthesis on a daily basis. The cognitive demands are likely to be higher during dual tasking. Different methods are suitable for quantification of cognitive load during dual tasking, for example, performance time and visual attention levels. For example, recent studies used eye-tracking systems as a tool to explore the gaze behavior when using a prosthetic hand during a grasping task and demonstrated that visual attention is focused more on the hand and grasping critical areas rather than on the object. Furthermore, when using an artificial hand, the time focused on the hand was longer. However, there are no documented findings of gaze behavior in a dual-task paradigm in prosthesis users. Therefore, in order to examine our hypothesis, we used a dual-task paradigm in two conditions: with VTF and without VTF. We aimed to evaluate the effects of adding VTF on the performance and visual attention of functional motor tasks in transradial amputees, using their myoelectric prosthesis in a dual-task paradigm.

Methods

The study was approved by the hospital Helsinki Committee (HMO-0099-16) and was registered in the ClinicalTrials.gov website (registration number NCT02749643). All subjects read and signed an informed consent pretrial.

The study took place at the Motor Function and Rehabilitation Lab at Tel Aviv University, Israel. Data were collected during the year of 2017 by a trained physiotherapist with experience in training myoelectric prosthesis users (E.R.).

We recruited 12 myoelectric prosthesis users using a convenience sample. The sample size was calculated using a software for power and sample size calculations (Power and Sample Size
Calculation software, Version 3.1.2; Department of Biostatistics, Vanderbilt University, USA). We performed a preliminary trial using a similar experimental setup with 43 non-impaired subjects, using a myoelectric robotic hand, which was controlled using electromyography (EMG) signals from the forearm muscles of the subjects. Our results showed that the standard deviation of our primary outcome measure, the performance time of the functional motor tasks, was 20% of the mean performance time. If the expected difference in the performance time between the trials with VTF and without VTF is 10%, then the calculated sample size is 10 subjects with power of 80% and $\alpha = 0.05$.

Inclusion criteria were unilateral transradial amputation patients, 18–70 years old, using a myoelectric prosthesis, with the ability to follow simple instructions, understand and sign an informed consent form, and with normal or corrected eyesight. The exclusion criteria were elbow or wrist disarticulation or partial hand amputations, neuropathy or skin ulcers on the amputated limb, and cognitive or mental deficits that limit the ability to participate fully in the study protocol. Table 1 depicts the personal and clinical characteristics of the study participants.

The study design is presented in Figure 1. All participants filled out three questionnaires: a personal and clinical characteristics questionnaire; the Orthotics and Prosthetics User Survey–Upper Extremity Functional Status (OPUS-UEFS), concerning the ability to perform daily tasks; and the Revised Trinity Amputation and Prosthesis Experience Scales (TAPES-R) questionnaire on psychosocial aspects of daily use of the prosthesis.

The dual-task paradigm was performed twice, once with the VTF activated and once without VTF. In order to prevent bias in learning the task, the study was performed in a counterbalanced order of the two conditions, so that half of the subjects started the trial with VTF turned on and repeated the trial when it was turned off and vice versa for the second half of the subjects (Figure 1).

The experimental setup is presented in Supplementary Figure A. Four thin force sensors (FlexiForce A201; Tekscan Inc., USA) were attached to the fingers and thumb of the myoelectric hand, in order to detect a gripped object (Supplementary Figure A, upper right). An elastic strap containing eight vibrotactile actuators (Shaftless vibration motor 10 × 2.0 mm; Pololu, USA) in its interior was wrapped around the arm, above the prosthesis (Supplementary Figure A, lower right). The vibrotactile actuators and controller unit (Arduino Holding, Italy) were powered by a small 3V rechargeable battery, with average power consumption of 320 mA (Miracase 2600mAh portable power bank; Hong Kong Miracle Technology Co., Ltd., China). The actuators were activated to their maximum amplitude when the applied force was above a threshold level. The threshold levels from the four force sensors were determined in the following pattern: below 17.6 N—no actuator was activated; between 17.6 and 41.2 N—one pair was activated; between 41.2 and 70.6 N—two pairs were activated; between 70.6 and 100 N—three pairs were activated; above 100 N—activation of all vibrotactile actuators. Thus, the tactile feedback generated by the actuators provided the subjects with binary information on the closing of the hand at a certain level of pressure, that is, on whether an object was held inside the hand. The feedback system was attached to the

| Table 1. Personal and clinical characteristics of the study participants (N = 12). |
|---------------------------------|-----------------|
| Gender                         | 11 males; 1 female |
| Age (years)                    | 65.0 ± 13.0     |
| Prosthesis hand type           | Eight regular myoelectric; four multiarticulated |
| Time since amputation (years)  | 43.0 ± 11.3     |
| Duration of prosthesis usage (hours per day) | 15.5 ± 6.0 |
| OPUS-UEFS questionnaire score  | 29.0 ± 2.5      |
| TAPES-R questionnaire score    | 8.4 ± 0.1       |

Quantitative values are presented as median and interquartile range.

myoelectric prosthesis of the subjects using Velcro straps (Supplementary Figure A, lower left).

During the trial, the subjects were seated in front of the computer screen and instructed to toggle the two arrow keys with their intact hand in order to keep an advancing virtual car on a marked path. A second task comprised five grasping tasks, for moving or manipulating objects of different sizes and shapes. During the trial, instructions for each grasping task appeared on the screen in the following order: (1) transfer the marker pen from the holder to the basket, (2) place the eraser in the trash bin, (3) transfer sugar with the teaspoon from the container to the glass, (4) mix the sugar in glass three times, and (5) place the key on the shelf. The dual-task paradigm combined playing the game with the intact hand while completing each functional task with the myoelectric prosthesis. The computer game was programmed using a commercial software (LabView version 13; National Instruments, USA). It recorded performance time of the grasping tasks and the time that the virtual car went off-road, as a percentage of the total game time, where a lower percentage reflects improved performance. The outcome measures for gaze behavior were the time which the subjects focused their gaze on the screen, as a percentage of the total trial duration. A high percentage of visual attention time indicated lower attention levels allocated to the myoelectric prosthesis. In addition, we calculated the number of times the subjects shifted their gaze from the screen to the myoelectric prosthesis during each of the five tasks.

The data were analyzed using a commercial statistical software (SPSS statistics, Version 21; IBM, USA). We used the Mann–Whitney U test to examine the counterbalanced order of the two conditions—*with VTF* and *without VTF* and (2) the accumulated time that the virtual car went off-road, as a percentage of the total game time, where a lower percentage reflects improved performance. The outcome measures for gaze behavior were the time which the subjects focused their gaze on the screen, as a percentage of the total trial duration. A high percentage of visual attention time indicated lower attention levels allocated to the myoelectric prosthesis. In addition, we calculated the number of times the subjects shifted their gaze from the screen to the myoelectric prosthesis during each of the five tasks.

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The data were analyzed using a commercial statistical software (SPSS statistics, Version 21; IBM, USA). We used the Mann–Whitney U test to examine the counterbalanced order of the two conditions—*with VTF* and *without VTF*. The Shapiro–Wilk test was used to assess the normality of distribution of continuous variables and showed that most outcome measures were normally distributed. In order to compare the outcome measures between the two conditions, that is, with and without VTF in all five functional tasks, we used a repeated-measures multivariate analysis of variance (MANOVA) analysis to counteract multiple comparisons. Results were considered statistically significant if $P < 0.05$. 

**Figure 1.** *Study design.* The study was performed in a counterbalanced order of the two conditions. Following a short training of grasping the objects and getting acquainted to the vibrotactile feedback, the subjects performed the dual-task paradigm twice, with and without vibrotactile feedback, with a short rest between the conditions.
Table 2. Mean values and standard deviation (in parentheses) of parameters in two conditions (with vs. without vibrotactile feedback).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Task</th>
<th>With feedback</th>
<th>Without feedback</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Performance time of motor task (seconds)</strong></td>
<td></td>
<td>93.2 ± 9.6</td>
<td>107.8 ± 20.3</td>
</tr>
<tr>
<td>Number of times the gaze shifted from the screen to the myoelectric hand</td>
<td>Transfer marker to basket</td>
<td>6.2 (3.0)</td>
<td>12.4 (9.2)</td>
</tr>
<tr>
<td></td>
<td>Throw eraser into trash bin</td>
<td>9.0 (6.0)a</td>
<td>7.3 (3.5)</td>
</tr>
<tr>
<td></td>
<td>Use a spoon to put sugar in a glass</td>
<td>7.0 (3.7)</td>
<td>8.6 (6.1)</td>
</tr>
<tr>
<td></td>
<td>Mix the sugar three times</td>
<td>5 (2.2)</td>
<td>7.3 (3.7)</td>
</tr>
<tr>
<td></td>
<td>Place the key on the shelf</td>
<td>5.3 (3.1)</td>
<td>6.0 (9.0)a</td>
</tr>
<tr>
<td>The time of applying visual attention to the screen (percentage of time to complete the task)</td>
<td>Transfer marker to basket</td>
<td>27.2 (19.6)</td>
<td>31.4 (15.5)</td>
</tr>
<tr>
<td></td>
<td>Throw eraser into trash bin</td>
<td>26.5 (14.2)</td>
<td>39.3 (25.0)</td>
</tr>
<tr>
<td></td>
<td>Use a spoon to put sugar in a glass</td>
<td>38.5 (30.2)</td>
<td>42.8 (27.6)</td>
</tr>
<tr>
<td></td>
<td>Mix the sugar three times</td>
<td>36.5 (29.0)</td>
<td>43.5 (27.9)</td>
</tr>
<tr>
<td></td>
<td>Place the key on the shelf</td>
<td>26.9 (18.0)</td>
<td>31.1 (26.6)</td>
</tr>
<tr>
<td>The total time that the virtual car was off-road (percentage of time of whole game)</td>
<td>51.4 (15.7)</td>
<td>50.2 (19.5)</td>
<td></td>
</tr>
</tbody>
</table>

*aMedian and interquartile ranges are presented where data are not normally distributed.

Results

The participants in our study were experienced prosthesis users, with a median of 43 years following their limb loss. The median duration of time for using the prosthesis per day was 15.5 hours (Table 1). All participants were also highly adjusted to using a prosthesis, both socially and physically, as was indicated by the high scores in the OPUS-UEFS and TAPES-R questionnaires (Table 1).

The results of the study parameters in the two conditions—with VTF and without VTF—are presented in Table 2.

A significant main effect was observed for VTF on total performance time ($F(1, 8)=7.69, P=0.024$; Table 2). When VTF was available, the total performance time required to complete the five functional tasks using the myoelectric prosthesis was significantly shorter compared with no VTF (93.2 ± 9.6 seconds and 107.8 ± 20.3 seconds, respectively; Table 2). This effect did not vary across the five different tasks, that is, no main effect was observed for the different functional tasks ($F(4, 32)=1.59, P=0.202$) nor for the interaction of task and VTF ($F(4, 32)=0.84, P=0.511$).

No main effect of VTF on performance was found with regard to the percentage of time the car went off-road during the game ($F(1, 11)=0.36, P=0.563$), so that the subjects were able to successfully perform the two tasks (driving game and grasping tasks) simultaneously in both conditions.

The use of VTF did not significantly affect patterns of gaze behavior as measured in our study. No significant main effect of VTF was found for the number of times the gaze shifted from the screen to the myoelectric hand ($F(1, 8)=5.04, P=0.055$), nor for the proportion of time devoting visual attention to the screen ($F(1, 8)=4.11, P=0.077$).

Discussion

In this study, we examined the effects of adding VTF to myoelectric prosthesis users on the performance time and gaze behavior in a dual-task paradigm. Our main finding was that adding VTF improves total performance time while dual tasking. There was no effect of adding VTF on the gaze behavior of the prosthesis users during performance of a dual-task paradigm.

As defined by Paas and colleagues, cognitive load is the total load that performing a particular
task imposes on an individual’s cognitive system. During grasping and manipulating objects in parallel with another task, that is, in a dual-task paradigm, the cognitive load is increased. When performing a task of daily life, for example, holding a cup while typing on a keyboard, cognitive efforts are needed in order to maintain efficient control, using visual and tactile resources.

For a transradial amputee, using a myoelectric prosthesis without tactile feedback, a dual-task paradigm poses a challenge. As shown in this study, dual tasking without tactile feedback results in increased time for task completion. Interestingly, conflicting results were found in a study where non-impaired subjects activated a virtual hand prosthesis with the addition of VTF. In this study, the dual-task paradigm comprised grasping a virtual object in a correct position and performing an auditory counting task. When VTF was available, the percentage of correct hand positions was improved, but performance time was increased. As noted by the authors, this increase in time may be due to a speed-accuracy trade-off, as the subjects performed significantly more accurately when using VTF, which was possible because there were no negative consequences for poor performance.

Another aspect of the cognitive load during a dual-task paradigm is the allocation of visual resources. A previous study correlated good performance levels in functional tasks with lower visual attention levels in experienced prosthesis users. In a recent study, it was found that non-impaired subjects using a prosthetic hand simulator focused their gaze on their hand, rather than on the manipulated object. Another study compared the gaze behavior while grasping and pouring water from a carton between non-impaired subjects and myoelectric prosthesis users. During reaching, prosthesis users allocated their visual attention extensively to their prosthetic hand and to areas critical to grasping the carton, while the able-bodied subjects focused less attention on their hand and more attention to the water carton. One suggested explanation for these findings was the inherent lack of tactile feedback from the prosthetic hand, compelling the user to allocate visual attention directly to the myoelectric hand in order to improve control during grasping.

In a recent study, we examined the effects of adding VTF to a myoelectric-controlled artificial hand simulator, used by non-impaired subjects to perform functional tasks in a dual-task paradigm. Similar to this study, we found no significant differences in the gaze behavior between the two conditions, that is, with and without VTF, during the dual-task paradigm. Our conclusion was that the non-impaired subjects might have difficulty in activation of the myoelectric-controlled hand, so that the possible effects of adding tactile feedback to myoelectric prostheses could not be deduced. Therefore, we examined this hypothesis in prosthesis users in our current study. We expected that when VTF is available for prosthesis users, they will allocate less visual attention to the myoelectric hand, allowing them to focus more on the screen. However, there were no significant differences observed in the gaze behavior between the condition where VTF was available or not. These results can be explained by the character of the grasping tasks chosen in our study. Except for one task, all tasks involved moving an object toward a specific target, for example, transferring a marker to basket or throwing an eraser into a trash bin. Therefore, the visual attention was required at the beginning and end of the task. Another possible explanation of our results can be related to the nature of the secondary task, which in our study was quite simple. Studies demonstrated that the performance levels of a visual search task in a dual-task paradigm depend strongly on task difficulty level. When investigating the visual performance during searching for a mismatch in two images in a dual-task paradigm, different levels of difficulty reduced the level of performance. Therefore, it could be that the secondary task of keeping the virtual car on track was too simple, so it did not pose a high cognitive challenge to the subjects. A more challenging secondary task might have produced different results of gaze allocation between with VTF and without it. Future studies may consider improving our dual-task paradigm, so that the secondary task is more difficult for the subject, for example, typing a sentence with the intact hand during grasping objects with the myoelectric hand. In that way, the cognitive workload
will be more distinctive, and the effects of adding VTF may be more detectable.

During object manipulation, gaze is usually directed to the object, the grasping site, and the target place. Gaze is allocated to each of these locations before the hand moves and stays there until the task is completed. Therefore, in future studies, it may be productive to examine the effect of adding VTF in tasks that do not involve move to target, for example, the task used in this study of mixing sugar in a cup, where the object is held and manipulated in a specific location without moving it to a target.

Our study has several limitations. The main limitation is its small sample size, so that the results might not apply to the larger myoelectric user population. Another limitation of our study is the character of the chosen grasping tasks. In our study, the subjects performed a set of five different tasks, for example, grasping a key, an eraser, and a marker. Over the years, several classifications of grasping types have been suggested. In addition to grasping types, daily tasks are differentiated by the shape of the grasped object, its specific size, weight, rigidity, and therefore grip force requirement. The characteristics of the grasping types and functional tasks selected for our study might have affected the results. Future studies may compare the effect of VTF on different grasping patterns, for example, cylindrical or tripod grasps, in order to better understand the role of tactile feedback in the grasping process of prosthesis users for different types of objects and tasks.

An additional limitation is the short learning time provided to the subjects for acquainting themselves with the VTF system. Since the subjects in our study were introduced to the VTF for the first time, they may not have internalized the feedback in such a way that they would choose to prefer it over their visual feedback. As a result, VTF did not play a significant role during the trials in reducing visual attention; however, our findings of reduced performance time suggest an immediate advantage provided by the feedback. Future studies may examine the effects of adding VTF to prosthesis users following a longer training period using VTF at home or work.

Another topic that may have affected our results is the habituation to the VTF, that is, the decrease in response to the tactile stimulus after repeated presentation. However, as pointed out by Wentink and colleagues, the habituation time to VTF provided by similar actuators to the ones used in our study is estimated to be 2–3 minutes. Since each grasping task in our study lasted up to 2 minutes, the presence of habituation in our study is unlikely. Furthermore, we used a feedback algorithm depending on force amplitude, that is, we changed the number of vibrating motors situated in different locations on the arm cuff according to the force measured by the force sensors. As a result, a sufficient change in the grip force produced a change in the vibration, which can help prevent the process of habituation. As in similar studies using VTF system for prosthesis users, we placed the vibrotactile actuators in a cuff wrapped around the arm. However, other studies exploring the effects of VTF on healthy subjects placed the actuators directly on the forearm. It may be more effective to place the actuators inside the prosthetic socket, which may present a more effective stimulus. Nevertheless, several technical difficulties may occur when placing the actuators inside the prosthesis, for example, sweat which can cause a malfunction, neuropathy of the residuum which can reduce the effect of the VTF, and mechanical disturbance to the reading of the EMG electrodes built inside the socket. Using the positive results of VTF in the literature and in our study, prosthesis manufacturers may consider adding VTF as an integral part of the socket.

In our study, we examined the effects of adding VTF to transradial amputees using a myoelectric prosthesis in a dual-task paradigm. However, results may differ when using a body-powered prosthesis, which is activated through cables and straps. It would be interesting to compare the effects of VTF between body-powered and myoelectric prosthesis users, since the provided feedback is different, as body-powered prosthesis users can utilize the proprioceptive feedback provided by the movement of the cables. As recommended in a review on the difference between the two types of prostheses, there is still a lack of evidence in this
topic, and there is a need of more structured studies.25

The results of our preliminary study have implications on the design and use of myoelectric prostheses. Several studies presented portable VTF systems, which were implemented into the hand prosthesis.23,24 When using these systems, the prosthesis users were able to improve their performance with regard to their grasp control, for example, holding objects without breaking them. If prosthetic hands will be provided in the future with inherent tactile feedback, this may profoundly change habits of using the prosthetic hand, allowing prosthesis users to perform complex daily tasks faster and possibly with reduced cognitive effort.

In conclusion, tactile feedback can be an effective addition to myoelectric prosthesis users, improving performance time during grasping and manipulating objects in a dual-task paradigm. Future research in the field of prosthetic rehabilitation may benefit from investigation of the effect of adding tactile feedback as an integral feature in hand prostheses, so that prosthesis users may achieve better performance of daily tasks, as well as reduce the cognitive demands during everyday situations.

Clinical Message
- When evaluating the effects of adding vibrotactile feedback to myoelectric prosthesis users in a dual-task paradigm, the performance time required to complete motor tasks was shorter with the feedback, but no difference was found in the gaze behavior.

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References


