Final Report:
Motor Training Induced Neuroplasticity across the Lifespan

- Suzanne und Hans Biäsch Stiftung -

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1 Final report

1.1 Introduction

A considerable amount of cognitive psychology literature has been published on the division of the two human memory compartments: the explicit and the implicit memory system (Schacter & Tulving, 1994; Squire, 1992). These two systems do have different capacities and different learning histories. A major point with respect to aging is the fact that these two memory systems are differently affected in old age (Fleischman, Wilson, Gabrieli, Bienias & Bennett, 2004). There is strong evidence that the implicit memory system is relatively good in acquiring new information even in older age while the function of the explicit system continuously diminishes. It has to be mentioned that motor learning is an important sub-division of the implicit system. Thus, a classical advice to older subjects is to practice the implicit system more frequently in order to strengthen this system for controlling everyday situations (Tilborg, Kessels & Hulstijn, 2011). However, the underlying neurophysiological mechanisms of this memory system to learn in older ages has not been subject to intensive research, so far. The present project focuses particularly on this system in order to examine the underlying neural mechanisms change as a consequence of a complex and intensive motor training.

Taken together, the present work aims to extend our knowledge about motor learning induced plastic adaptations of the human brain.

1.2 Aims and research questions of the present project

Hotel Plastisse is an iPad-based cognitive training app conceptualized for older adults. With this study, which is imbedded in the *Hotel Plastisse* project (see 1.3.3 Complex visuo-motor training), we aim to investigate the underlying neurophysiological mechanisms of the complex visuo-motor iPad tasks. The neurophysiological correlates of the complex visuo-motor tasks are measured by means of high-density Electroencephalography (EEG). A second aim of this study concerns the investigation of behavioral and neurophysiological differences between *Hotel Plastisse* training "experts" (i.e. subjects participated in a former *Hotel Plastisse* study and are thus familiar with the viuso-motor training) and control subjects (i.e. participants that are not familiar with the *Hotel Plastisse* visuo-motor training tasks). Furthermore, we are interested in the relationship between learning performance (behavioral data from 50 training sessions) and EEG measures, such as frequency bands and network characteristics.

The motivation for these aims bases on previous research investigating training-induced neuroplasticity of the motor system (Koeneke, Lutz, Esslen & Jäncke, 2006; Bezzola, Mérillat & Jäncke, 2012a; Dayan & Cohen, 2011) in old age. By reviewing the literature the previous motor training paradigms can be divided in two types of training: Either

simple motor trainings (e.g., simple finger training) or complex motor trainings (e.g., visual perception and fast finger movement simultaneously). Both training approaches have their positive and negative aspects. However, it needs to be mentioned that the former facilitates high experimental control but depicts a very distinct and small aspect of the motor system. In contrast, the majority of complex motor trainings lack experimental control. This issue leads to a gap in the pertinent motor training research, namely a complex motor training approach with a high internal and external validity. The *Hotel Plastisse* app offers an elegant tool to investigate complex motor and cognitive functions without having losses in experimental control.
The present study includes the following research questions and hypotheses:

1. Which EEG frequency bands play an important role in performing a distinct *Hotel Plastisse* visuo-motor task?

→ Considering recent studies, we expect in particular the alpha (and mu) frequency band to play an important role in performing the visuo-motor tasks.

2. Which anatomical regions are most relevant in performing the visuo-motor tasks successfully?

→ We expect to find activations in visuo-motor cortical regions (parietal cortex, pre-motor cortex).

3. Do the relevant frequency bands differ between the visuo-motor training-group and the control group?

→ We expect group differences in the mu frequency band.

4. Do network characteristics differ between the visuo-motor training-group and the control group?

→ We expect a group effects in the parameter path length and clustering coefficient.

5. Are learning performance and EEG measures related to each other?

→ We expect a relationship between learning performance and EEG measures. However, this question/hypothesis needs to be elaborated more precisely.

1.3 Methods

1.3.1 Study sample

The experimental group (n=16) of the present study consists of older participants between the age of 65 and 75 years. These 16 participants are subjects of a former *Hotel Plastisse* study (green color in Figure 1) and are thus familiar with the visuo-motor training. In addition to data from the training group, also data from a passive (n=23) control group was collected. Participants from the passive control group were age- and gender-matched to the training group and had no pre-experience with the *Hotel Plastisse* training software.

1.3.2 Experimental design

The present study investigated training-induced neuroplasticity of the *Hotel Plastisse* training app by means of a cross-sectional experimental design. Since, the participants of the training group were recruited from a former study, the present data collection of this group was also a follow-up session (i.e., as part of a longitudinal study) and simultaneously a cross-sectional EEG session (see Figure 1).
It should be mentioned that a longitudinal study design would be more suitable, in particular when investigating complex motor learning and developmental processes. By integrating the present cross-sectional study into a former longitudinal *Hotel Plastisse* study we tried to take this issue into account. The combination of the two studies, meaning the combination of a cross-sectional and a longitudinal study design, allows us to investigate complex motor learning in more detail (compared to a cross-sectional design, only). First, behavioral training data (i.e. longitudinally collected data of 50 training sessions) can be used in order to analyze the relationship between different learning slopes and neurophysiological data. Research question 5 focusses on the relationship between learning curves and neurophysiological data. Second, this design allows also to analyze group effects. Group differences are relevant for research questions 3 and 4.

1.3.3 Complex visuo-motor training

The *Hotel Plastisse* Software is an iPad-based serious training game, developed in collaboration between the International Normal Aging and Plasticity Imaging Center (INAPIC) at the University of Zurich and the Zurich School of Arts (Figure 2). This training app is particularly conceptualized for older adults and includes four different trainings: (1) visuo-motor training, (2) spatial training, (3) inhibition training, and (4) multi-domain training (i.e., training three functions (1-3) simultaneously). Each training consists of 5 training tasks (so called mini-games) and lasts approximately 45 to 60 minutes. The training consists of 50 training sessions (10 weeks, 5 sessions per week). The difficulty level of the training was adaptive and each training session included a feedback of the daily performance. After each session the behavioral data (i.e. a highscore file) of the tasks were uploaded on a data server.
The visuo-motor training included the following mini-games:

- *Rollobst*: Visuo-motor task performed with the right index finger (Figure 2)
- *Murmelspiel*: Bi-manual visuo-motor task

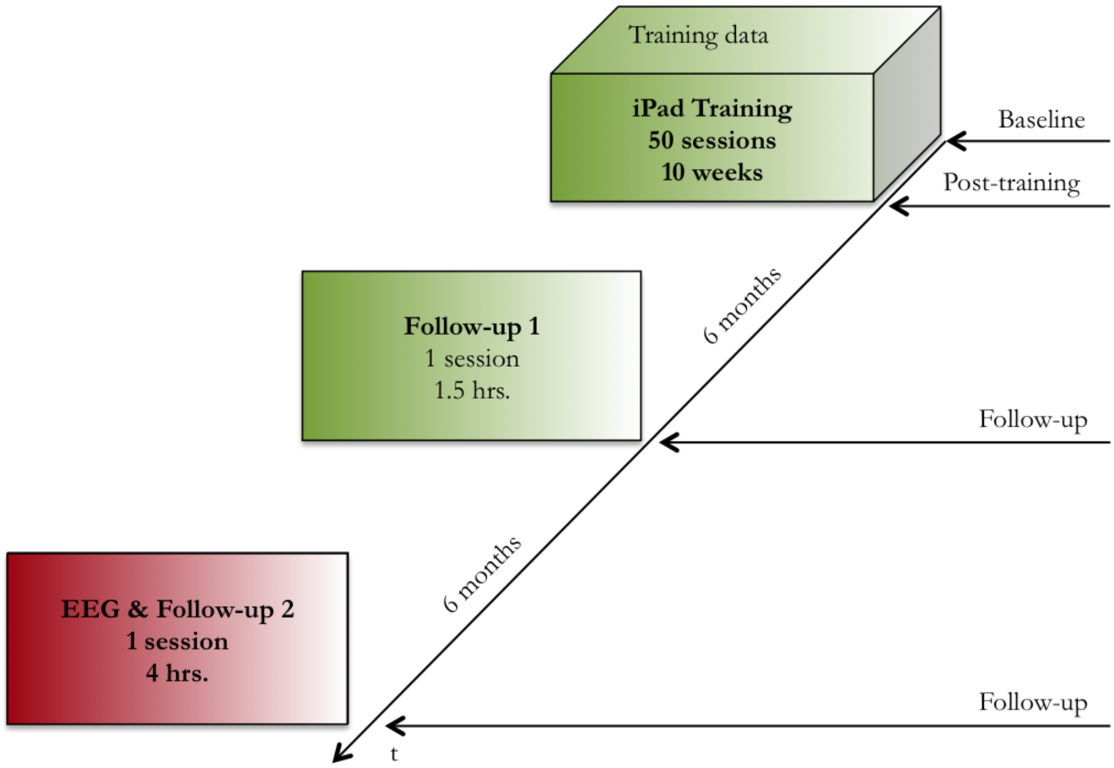

Figure 1: Experimental design with the measurement time-points. The training group run through all measurement time-points (green = former study; red = present EEG study). The control group run only through one measurement time-point (red).

- *Modellflugzeug*: Bi-manual visuo-motor task

- *Hundepfoten*: Visuo-motor task performed with the right index finger

- *Pfeilwerfen*: Bi-manual visuo-motor task

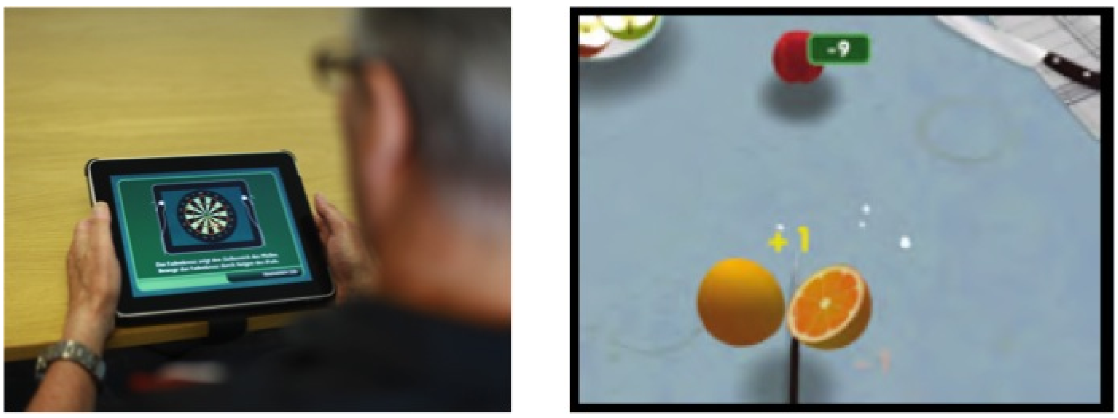

Figure 2: Left: A participant playing the iPad-based *Hotel Plastisse* training app. Right: The visuo-motor *Rollobst* task. The rolling fruits need to be cut, by moving the knife with the index finger as precisely as possible.

1.3.4 Outcome measures

The EEG method was applied, in order to investigate the neurophysiological correlates of the visuo-motor *Hotel Plastisse* tasks. The non-invasive method of EEG enables to depict the neuronal activity with a high temporal resolution while performing an iPad-based visuo-motor task without inducing artifacts on the EEG signal. Other imaging methods, such as magnetic resonance imaging (MRI), are highly susceptible to various artifacts induced by electrical devices and do not allow the simultaneous investigation of an iPad-based task and the measurement of neuronal activity.

With this project we collected a broad range of behavioral and EEG measures. The participants went through a measurement session that lasted approximately 4 hours. Figure 3 shows the procedure of one single session. This report focuses primarily on the results of two unimanual performed visuo-motor tasks (behavioral performance and EEG measures), namely the so called *Rollobst* task performed with the right hand (i.e., a trained visuo-motor task for the training group) and the same task performed with the left hand (i.e., untrained task for both groups). This task allows to investigate training-induced effects (e.g., lateralisation effects) as well as general neurophysiological underpinnings.

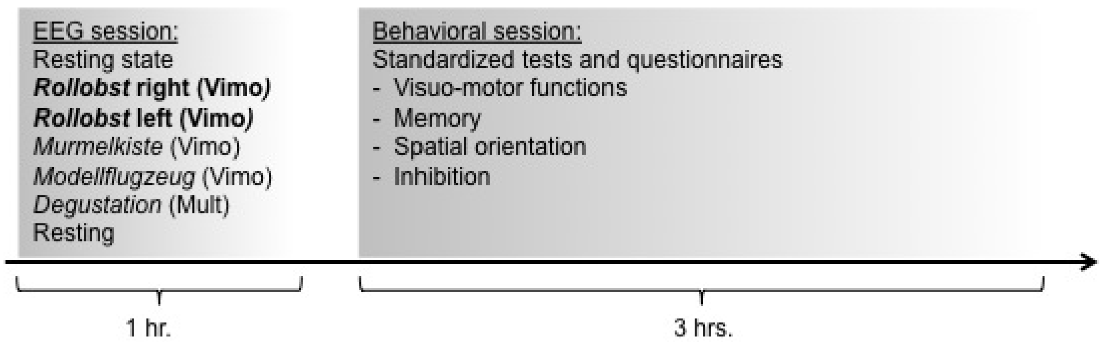

Figure 3: A standardized measurement session including EEG (Vimo = visuo-motor tasks; Mult = multi-domain task) and behavioral data collection. The two *Rollobst* tasks (bold) are the focus of the present report.

<u>EEG measurement</u>

Subjects performed visuo-motor tasks (Vimo), a multi-domain task (Mult) and two resting-state "tasks" while EEG data were recorded (see Figure 3). The EEG measurement took place in a sound-shielded Faraday cage and lasted approximately 1 hour. High-density EEG was recorded with a 256-channel EEG Geodesic Netamps system (Electrical Geodesics, Eugene, Oregon). Prior to the EEG-data analysis the data needed first to be pre-processed, including a variety of different steps (e.g., data filtering, eye movement and heart rate artifacts were removed by running an ICA, rereference, etc.). The preprocessing is needed in order to eliminate interfering signals. The artifact free EEG was then segmented into 2s epochs (Langer, Bastian, Wirz, Oberauer & Jäncke, 2013). In a further step a Fast-Fourier transformation was applied in order to calculate the power spectrum from 1.5-49.5 Hz. The average spectrum over all epochs was then the major outcome measure (i.e., dependent variable). The present report focuses primarily on alpha band activity, meaning the frequency band between 8-13 Hz. This frequency band has shown to play an important role in motor tasks (Pfurtscheller, Neuper, Andrew & Edlinger, 1997). As mentioned earlier (complex visuo-motor training) data on the behavioral performance of the visuo-motor task was collected simultaneously, allowing a precise control of the performed iPad task. The main outcome measure here was the percent correct responses. We performed for both outcome measures (EEG averaged alpha activity and percent correct responses) and both tasks (left and right hand motor task *Rollobst*) a repeated-measures ANOVA with within-subject factor hemisphere (left hemisphere, right hemisphere) and between-subject factor group (training group, control group).

Behavioral measurement

The test battery of the behavioral measurement included the same tests as the former *Hotel Plastisse* study. A behavioral measurement session lasted approximately 3 hours. Besides various questionnaires also standardized tests were applied in order to test visuo-motor functions, inhibition, spatial orientation, memory and attention. Since the scope of the present report lies on the EEG analyses a detailed description of the used tests can be found elsewhere (Binder et al., 2015).

1.4 Short summary of the results

The present report focusses on the results of one distinct motor task of the *Hotel Plastisse* app, namely the so called *Rollobst* task. One run was performed with the right hand, the other run was performed with the left hand. The investigation of both, a trained task (i.e., task performed with the right hand) and an untrained task (i.e., task performed with the left hand), allows to focus on two lines of research questions. First, when focussing on the right hand motor task, research questions considering group differences are possible (i.e., research questions 3, 4, 5). The second line of research, investigates the general neurophysiological underpinnings of the visuo-motor task independent of training expertise by analyzing the visuo-motor task performed with the left hand (i.e., research question 1, 2). The present report includes only preliminary results, meaning that we first aimed to investigate the general underpinnings of the motor task and as a further main aim we examined group differences.

1.4.1 General neurophysiological underpinnings of *Hotel Plastisse*

There is strong evidence that especially the mu-rhythm (in the range of alpha frequency 8 - 13 Hz. localized over the sensorimotor system) plays an important role in motor and visuo-motor related tasks (Pfurtscheller & Neuper, 1997). This rhythm is however attenuated when motor outputs are processed, meaning that during a movement phase the mu-rhythm is desynchronized (Pfurtscheller et al., 1997). In other words, a system with a high mu-activity indicates that the sensorimotor system is in a idling mode. Corresponding to these previous research investigating the EEG correlates of the motor system, we hypothesize especially the mu-/ alpha-frequency band to play an important role while performing the visuo-motor *Hotel Plastisse* task. Accordingly, the activity is expected in electrodes localized over the sensorimotor cortex.

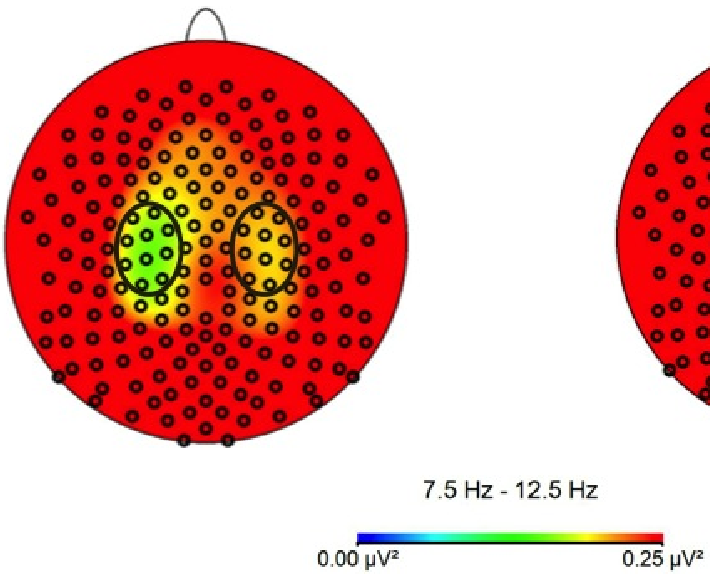

Figure 4: Topographical maps for the right hand task and the left hand task. Plotted is the frequency range between 7.5 and 12.5 Hz. The left and right sensorimotor cortex (SMC) ROI include 10 electrodes (solid line).

As can be seen in Figure 4 the frequency range between 7.5 and 12.5 Hz., i.e. the alpha frequency band, is particularly depicted in electrodes over the sensorimotor regions. This pattern is found for both tasks, the one performed with the right hand and the one performed with the left hand. This result indicates that the mu-rhythm, which is of particular relevance for sensorimotor tasks, plays also a major role in the present *Hotel Plastisse* task. Based on these general results the following analyses (i.e., group differences) take a closer look on the mu-activity over sensorimotor regions, including 10 electrodes per hemisphere.

1.4.2 Group differences

In respect to the group specific research questions, previous research investigating the neuronal underpinnings of motor learning demonstrated that in particular the inter-hemispheric interactions are highly plastic, which may be reflected in a training-induced changed lateralization pattern (Takeuchi, Oouchida & Izumi, 2012). Based on this former research, we hypothesized that the training group will show an interaction effect when performing the right hand motor task but not when performing the untrained left hand motor task.

First, we revealed a significant interaction effect (hand x group) on behavioral level ($F(1{,}36)=6.35$, $p<.02$). Subsequent paired t-tests showed that the training group outperformed the control group in the trained task but not in the untrained task (i.e. left finger task). This pattern was also reflected on neurophysiological level. The repeated measures ANOVA revealed a significant interaction (hemisphere x group) in the right finger task ($F(1{,}36)=4.75$, $p<.04$). Further analyses (i.e. paired t-tests) revealed increased mu-activity over sensorimotor regions in the training group compared to the control group (Figure 5). However, this finding was not present in the task performed with left finger.

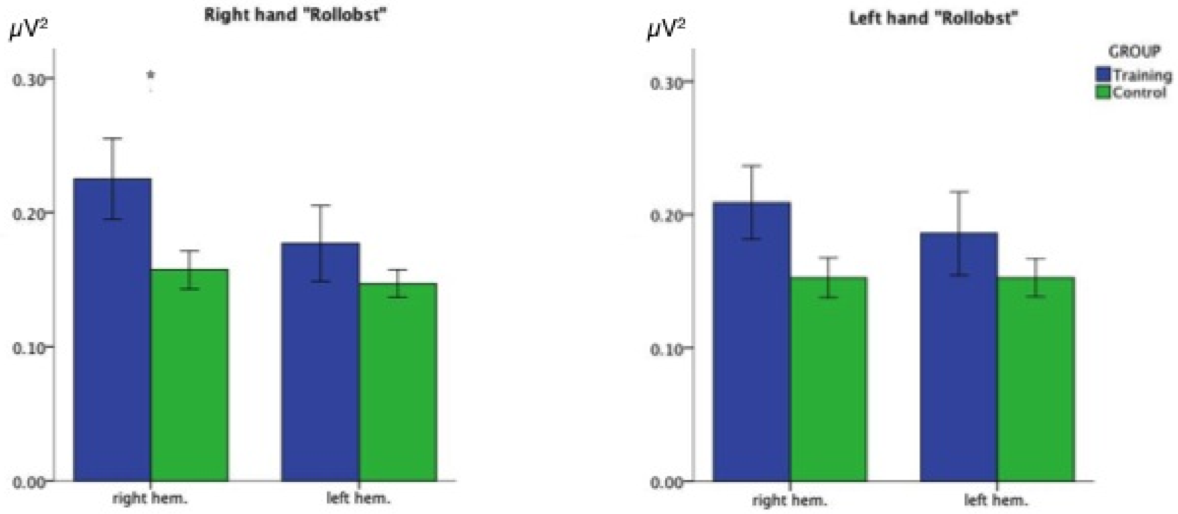

Figure 5: Two ANOVAs for right and left hand visuo-motor task. Y axis displays alpha frequency in μV^2 and x axis displays the right and the left SMC ROIs.

Here the repeated measures ANOVA (Figure 5) revealed a non-significant interaction effect (hemisphere x group; $F(1{,}36)=2.48$, $p>.10$).

From data in Figure 6 it is apparent that right finger task induces increased right-hemispheric mu-activity (i.e., alpha activity over sensorimotor regions) in the training group. This group effect is not apparent in the left hemisphere.

1.5 Conclusion

As a more general result, we show for the first time that the EEG method is a suitable method to study the underlying neurophysiological mechanisms of the *Hotel Plastisse* app. As expected the motor task relevant frequency band, has been show in a range between 8 and 13 Hz., localized in electrodes over the SMC. This result goes along with

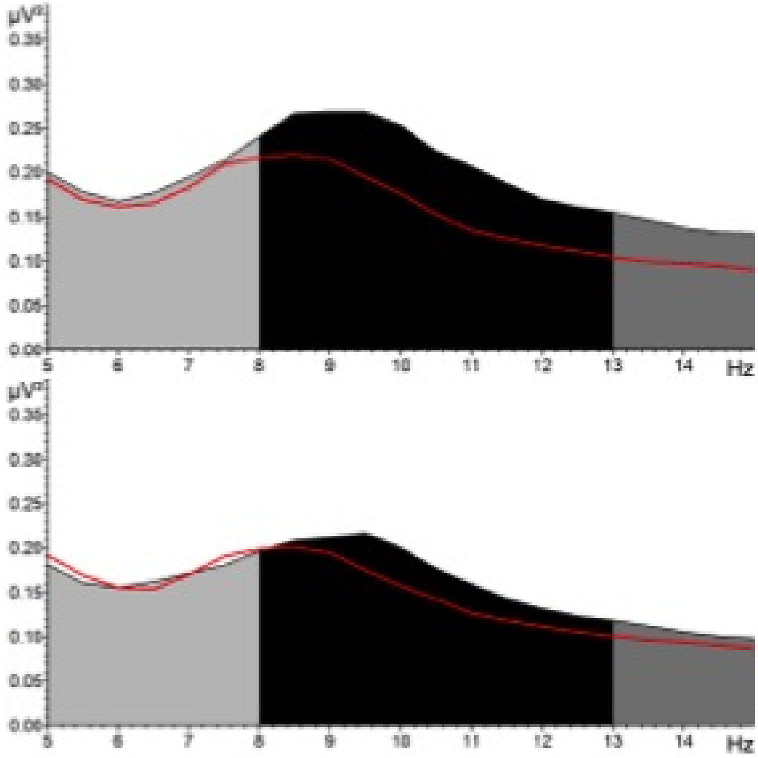

Figure 6: Spectral power for the alpha frequency range (black line = training group; red line = control group), while performing the right
hand motor task for the right (upper) and left (lower) hemisphere.

previous literature (Pfurtscheller et al., 1997) showing that the mu-frequency band is a prominent correlate in motor and visuo-motor tasks.

In the present work, neurophysiological correlates of a complex visuo-motor task have been investigated using the non-invasive EEG-method. The present findings indicate a group-difference that is specific to the task trained beforehand and emphasize the highly plastic processes on neuronal and behavioral level underlying a complex visuo-motor training in old age. As a main result of this study, we demonstrate that the complex motor task of *Hotel Plastisse* induces higher mu-activity, even a year after the training has been conducted. Higher mu-activity goes along with neuronal idling, meaning that the sensorimotor system of the training group may inhibit task-irrelevant processes more efficiently (Whitmarsh, Nieuwenhuis, Barendregt & Jensen, 2011). This effect showed to occur in the right-hemispheric (i.e., non-dominant) SMC. It is known, that the ipsilateral activity is especially important for difficult motor tasks (Chen, Gerloff, Hallett & Cohen, 1997). Therefore, one could assume that the reduced task difficulty in the training group might require less neuronal effort and mobilize more neuronal idling in the non-dominant hemisphere.

1.6 Outlook

Regarding the visuo-motor *Rollobst* tasks, additional analyses will be conducted in order to take a closer look on neurophysiological network characteristics (Langer et al., 2013; Binder, Bezzola et al., 2016 (manuscript under review)). Furthermore, data from the former *Hotel Plastisse* will be incorporated in the present findings. These additional analyses allow to elaborate research questions 4 and 5 in more detail. By including data from the former *Hotel Plastisse* training study, we take a closer look to the relation between behavioral (i.e. learning parameters) and neurophysiological measures. This issue has been emphasized in a recent study (Supekar et al., 2013), however this study focused on neuroanatomical measures (i.e., magnetic resonance imaging parameters). With the present study we aim to extend these previous findings, by focussing on neurophysiological measures (i.e., EEG data).

As can be seen in Figure 3, we collected data from additional EEG tasks, including *Hotel Plastisse* tasks and resting state. The latter, will be the next main focus of the present project. Additionally to the main research questions (mentioned earlier), pre-post analyses will be conducted for the resting state data. Thus, a short-term longitudinal analysis is possible and this analysis may shed more light on temporal aspects, such as cognitive fatigue, while conducting the *Hotel Plastisse* training.

2 Major changes to the original research plan

Do to several reasons, the original research plan needed to be adopted. First, the original research plan included three age groups, ranging from young adults over middle adulthood to old age. However, this age comparison goes along with a large N, since each group needs an appropriate size of study participants. The original research plan included 6 groups (3 age groups, 3 age-matched control groups) with 25 participants per group, resulting in a total N of 150 participants. The critical threshold of financial expenses and time exposure would have been exceeded, by including all participants in a training routine. Hence, with the present project we focused on the old age group. This age group, is the main focus at the INAPIC and the URPP Dynamics of Healthy Aging. Second, with the original research plan we planned to apply the method of structural and functional magnetic resonance imaging. This change (change from MRI to EEG), is supported by the fact, that the EEG method allows to acquire neurophysiological data while the participants perform the task on the iPad. The simultaneous data collection and performance of the training would not have been possible with the strict MRI requirements. However, this issue went along with a minor adaption of the research questions, namely a shift from neuroanatomical research questions to neurofunctional research questions.

With this major changes, I was able to to conduct a training study in my preferential research area, namely the neuronal correlates of motor training-induced neuroplasticity (Bezzola et al., 2012a; Bezzola, Mérillat & Jäncke, 2012b; Bezzola, Mérillat, Gaser & Jäncke, 2011). Hereby, I acquired additional methodological knowledge in an another neuroimaging method. This additional knowledge is a good complement to the previous studied methods.

References

Bezzola, L., Mérillat, S., Gaser, C. & Jäncke, L. (2011). Training-induced neural plasticity in golf novices. *Journal of Neuroscience*, *31*(35), 12444–12448.

Bezzola, L., Mérillat, S. & Jäncke, L. (2012a). Motor Training-Induced Neuroplasticity. *GeroPsych: The Journal of Gerontopsychology and Geriatric Psychiatry*, *25*(4), 189–197.

Bezzola, L., Mérillat, S. & Jäncke, L. (2012b). The effect of leisure activity golf practice on motor imagery: an fMRI study in middle adulthood. *Frontiers in Human Neuroscience*, *6*, 67.

Binder, J. C., Zöllig, J., Eschen, A., Mérillat, S., Röcke, C., Schoch, S. F., Jäncke, L. & Martin, M. (2015). Multi-domain training in healthy old age: Hotel plastisse as an ipad-based serious game to systematically compare multi-domain and single-domain training. *Front Aging Neurosci*, *7*, 137.

Chen, R., Gerloff, C., Hallett, M. & Cohen, L. G. (1997). Involvement of the ipsilateral motor cortex in finger movements of different complexities. *Ann Neurol.*, *41*(2), 247–254.

Dayan, E. & Cohen, L. G. (2011). Neuroplasticity subserving motor skill learning. *Neuron*, *72*(3), 443–454.

Fleischman, D. A., Wilson, R. S., Gabrieli, J. D. E., Bienias, J. L. & Bennett, D. A. (2004). A longitudinal study of implicit and explicit memory in old persons. *Psychology and aging*, *19*(4), 617–625.

Koeneke, S., Lutz, K., Esslen, M. & Jäncke, L. (2006). How finger tapping practice enhances efficiency of motor control. *Neuroreport*, *17*(15), 1565–1569.

Langer, N., Bastian, C. C. von, Wirz, H., Oberauer, K. & Jäncke, L. (2013). The effects of working memory training on functional brain network efficiency. *Cortex; a journal devoted to the study of the nervous system and behavior.*

Pfurtscheller, G. & Neuper, C. (1997). Motor imagery activates primary sensorimotor area in humans. *Neuroscience letters*, *239*(2-3), 65–68.

Pfurtscheller, G., Neuper, C., Andrew, C. & Edlinger, G. (1997). Foot and hand area mu rhythms. *International Journal of Psychophysiology*, *26*(1-3), 121–135.

Schacter, D. & Tulving, E. (1994). *Memory systems.* Cambridge: MIT Press.

Squire, L. R. (1992). Declarative and Nondeclarative Memory: Multiple Brain Systems Supporting Learning and Memory. *http://dx.doi.org/10.1162/jocn.1992.4.3.232*.

Supekar, K., Swigart, A. G., Tenison, C., Jolles, D. D., Rosenberg-Lee, M., Fuchs, L. & Menon, V. (2013). Neural predictors of individual differences in response to math tutoring in primary-grade school children. *Proceedings of the National Academy of Sciences of the United States of America*, *110*(20), 8230–8235.

Takeuchi, N., Oouchida, Y. & Izumi, S.-I. (2012). Motor Control and Neural Plasticity through Interhemispheric Interactions. *Neural Plasticity*, *2012*(6), 1–13.

Tilborg, I. A. van, Kessels, R. P. & Hulstijn, W. (2011). How should we teach everyday skills in dementia? A controlled study comparing implicit and explicit training methods. *Clinical rehabilitation*, *25*(7), 638–648.

Whitmarsh, S., Nieuwenhuis, I. L. C., Barendregt, H. P. & Jensen, O. (2011). Sensorimotor Alpha Activity is Modulated in Response to the Observation of Pain in Others. *Frontiers in human neuroscience*, *5*, 91.