Short scientific report for the STSM "The Efficiency of Neurofeedback in the Treatment of Chronic Tinnitus", BM1306_27140

Purpose of mission

The goal of this scientific mission was to apply and extend my knowledge and experience in the treatment of chronic tinnitus with tomographic neurofeedback. The advantage of tomographic neurofeedback compared to its classical form where only a few electrodes are used for measuring and feeding back brain activity is the significantly improved spatial resolution. This is enabled by combining it with the elaborated source estimation algorithm sLORETA (Pascual-Marqui, 2002) which makes more precise training in distinct brain regions (such as the primary auditory cortex) possible. Since currently a substantial clinical study at the University of Zurich in cooperation with the ORL day care unit of the University Hospital Zurich is planned where the superiority of the tomographic method shall be proven and which is based essentially on previous research findings of the STSM host and his group about tinnitus-specific oscillations in the resting brain (Dohrmann et al., 2007; Hartmann et al., 2013; Lorenz et al., 2009; Moazami-Goudarzi et al., 2010; Weisz et al., 2005, 2007a,b), I thus intended to improve my knowledge about the crucial factors for tinnitus treatment with (tomographic) neurofeedback during my two-week stay at the University of Trento. I consider the expert knowledge of Prof. Weisz and his group to be of utmost importance for the upcoming clinical study as they provided me with the necessary background information and technical know-how in order to significantly improve the quality of the planned clinical study in Zurich.

Description of the work carried out during the mission and the main results obtained

Week 1:

As already laid down in the detailed work plan in the application process, in the first week two comprehensive oral presentations were given in MEG group meetings at Nathan Weisz' MEG laboratory in the Center for Mind/Brain Sciences (CIMeC). While one was mainly dealing with the main results and conclusions of a pilot study conducted in Zurich in the scope of my master thesis, the other one laid down the details and design of the aforementioned more substantial clinical project which is planned to start as soon as possible.

In the pilot project I have already worked with tomographic neurofeedback and the sLORETA-based neurofeedback software has been tested extensively for the first time in the context of tinnitus treatment. Five patients participated in 15 training sessions whereby their resting-state EEG activity was measured and compared prior and after the trainings. The applied neurofeedback protocol measured activity in the primary auditory cortex and aimed at suppressing oscillations in the θ- band and in the lower γ- band while reinforcing α- power. Since statements about statistical significance were rather limited due to the small sample size, the

focus was laid rather on the gaining of experiences with the new software and numerous important conclusions could be drawn in regard of future projects.
It was highly interesting to present my master thesis project to a group consisting of so many well-known and established scientists who themselves have contributed to it in fundamental ways since the study was strongly based on previous research findings of Nathan Weisz and his group. The audience showed immense interest in the neurofeedback software used in the project. Being to date the only scientists in the world of tinnitus research that ever have conducted a tinnitus study with the tomographic form of neurofeedback by using software they developed and programed themselves (Hartmann et al., 2011; Hartmann et al., 2013), they were astonished by the technical advances and improvements in neurofeedback technology. It therefore came as no surprise that the input received in the subsequent discussions were highly illuminating for me. Many questions that still remained unclear after this project could be answered such as the issue of why alpha oscillations were clearly diminished after the training compared to the baseline even though an improvement had been targeted. It was suggested that this may be due to the failure of the rewarding feedback in our study since the controlling of the feedback procedure got substantially harder for the subjects the more reward-feedback was applied. This must inevitably have led to an implicit mind-set for the patients to not get as much reward in order to be able to control the feedback more easily.
This is only one example of the many fruitful inputs that were given during and after my presentation.

A slightly different neurofeedback protocol will soon also be used in the more substantial clinical study where 52 tinnitus patients will be treated with neurofeedback. Before my 2-week stay in Trento, however, many factors still remained unclear. Among those were considerations regarding the appropriate location of training as well as about which are the most crucial frequency-bands for tinnitus-alleviating neurofeedback training. Our group strongly tended to perform the feedback based on primary auditory cortex activity, however only focusing on the enhancement of α- power while neglecting the abnormalities found in γ- and δ-bands since alpha generally showed the most consistent results in this context.
After having presented the detailed design of the planned study which will be part of my PhD-project in Zurich and a quick demonstration of the neurofeedback setup, the hosts Prof. Dr. Nathan Weisz and Dr. Thomas Hartmann agreed on giving additional feedback in a more informal meeting. We quickly came to the same conclusion, namely that in the planned study the focus should be laid on altering the neural activity of the primary auditory cortex exclusively since in their prior studies unambiguous and stable differences in brain oscillations between tinnitus patients and healthy controls had been found in this area. Even though abnormalities were also observed in other brain regions of tinnitus patients, it remains unclear whether they are in fact involved in the emerging of tinnitus itself or should rather be seen as a consequence of this phenomenon.
Regarding the frequencies that should be included in the feedback, Mr. Weisz strongly suggested that the neurofeedback protocol should also include a reduction of δ- band activity instead of merely enhancing α-power. According to theory and empirical findings the increase of δ- and the decrease of α- oscillations in the auditory cortex of tinnitus patients go hand in hand and are strongly dependent on each other. Trying to alter one of them therefore will in-

evitably also lead to changes in the other which makes a training of both frequency bands simultaneously highly recommendable.
Furthermore, the two scientists referred to the work of Marco Congedo in Grenoble (F) who is about to developed a new method of neurofeedback, namely *independent component analysis (ICA) neurofeedback* (Congedo, 2010; Kopřivová, 2013), and plans to perform a tinnitus treatment study with this method in the near future. An extensive literature research brought many results and some time was also spent in the reading in this so far shamefully overlooked neurofeedback method.
Another interesting idea that was suggested was the performing of tinnitus treatment with neurofeedback in a form of bottom-up like approach, a method Nathan Weisz has already worked with during his time at the University of Lyon. In this approach tinnitus patients are connected to an EEG- and neurofeedback system and instructed to instantly report as soon as their tinnitus percept undergoes significant changes. The operator then systematically changes different frequency bands and locations for training in order to discover other hot-spots and important frequency abnormalities in the brain of tinnitus patients for neurofeedback treatment. This can be regarded as a highly explorative attempt since it is not or only partially based on empirical findings. It will therefore not be possible to include this idea in the upcoming clinical project but it will certainly be considered in future projects.
Also several other essential factors of the training setting such as quantity, duration and frequency of training sessions as well as the controlling of confounding factors have been discussed and several alterations will be made for the planned neurofeedback study. In the end we all agreed that the development and testing of individually tailored feedback protocols for different subtypes of tinnitus is the ultimate goal of neurofeedback treatment for chronic tinnitus patients and the planned study clearly can be seen as a first step in this direction.

In the course of the first week, it was agreed that the planned re-analysis of EEG-data obtained in the pilot study will not be performed since the study was mainly aiming at the gaining of experiences with the (at that time still completely unknown) neurofeedback software Cygnet and the data therefore were rather of secondary concern. Instead, I had the chance to observe all the members of the CIMeC-group while they were doing their research and to learn about their current work and future projects. Thereby, I came in contact with a lot of interesting research topics and, even more important, new data acquisition and analysis methods which certainly have broadened my knowledge and provided me with additional know-how to start my PhD-project. The chance to interact with so many established scientists as well as other PhD students from a multitude of different backgrounds in the fascinating world of neuroscience provided me with the opportunity to expand my personal, cultural, as well as scientific horizon.

Week 2:

In the second week of my stay at the University of Trento, I mainly focused on observing and assisting in MEG real-time experiments and data analysis in order to determine whether MEG may be a meaningful addition to future plans in Zurich. MEG is a very common research method in tinnitus research and neuropsychology in general which so far has been utterly ne-

glected in Zurich and, to my knowledge, even in all of Switzerland mainly due to its high costs for acquisition and maintenance. It is hard to put into words the enormous benefit that this unfortunately very short peek into the world of MEG-research offered me for my future research career. The most interesting and relevant advantage of MEG for the planned neurofeedback project can be seen in the superior spatial resolution compared to EEG since it generally works with individual head models and more recording channels. On that account, the head of every subject is usually strictly measured out with several sensors that transmit the position of each measuring point to the recording software. This information can be used for an appropriate positioning of the head during MEG acquisition as well as for the determination of sources of neuronal activity in the subsequent process of data analysis. In my opinion it can be seen as one of the major drawbacks of EEG source estimation techniques such as sLORETA that no individual head models are used but rather templates created from averaging many different brain scans. This makes source estimation certainly less accurate in each individual case and for neurofeedback training one can never be sure how well the auditory cortex of the subject really coincides with the standard brain. I therefore think of MEG as a very powerful method in order to determine neuronal sources of surface based activity which makes it in this regard clearly superior to perform and/or evaluate neurofeedback training in tinnitus patients.
For processing of the recorded MEG data the Center for Mind/Brain Sciences (CIMeC) provides a very useful wiki-page which provides step-by-step instructions on how to deal with MEG- (as well as EEG-) data with the Matlab-based toolbox *Fieldtrip* (https://wiki.cimec.unitn.it/tiki-index.php?page=DataAnalysisMain). Furthermore, various data sets are offered for free download in order to test the described steps of data analysis hands-on. Since I was rather inexperienced in data processing based on Matlab and Fieldtrip, the chance was taken to learn as much as possible in the use of these very essential and generally widely used analysis tools. With the knowledge I had the chance to gain, I am very confident that these tools will also be used in my upcoming PhD project.

Future collaboration with the host institution

Since the group of Prof. Weisz intends to move to University of Salzburg in November, no further collaboration with the host institution itself, the University of Trento, seems to be possible and necessary. However, Mr. Weisz indicated his greatest interest in the further progress of our neurofeedback project in Zurich and would very much like to hear about first results and developments. Furthermore, MEG seems to be a very feasible method to investigate the neurophysiological characteristics of chronic tinnitus mostly because of its high spatial resolution and the working with individual head models. It is thus highly possible that a combination of neurofeedback with MEG (either in the application of feedback itself or in the evaluation of possible effects in pre-post comparisons) will prove to be fruitful, which would make further cooperation with Prof. Weisz' group in Salzburg very interesting and desirable.

Foreseen publications/articles resulting from a mission

Due to the limited time of the short term scientific mission no publications are intended.

Confirmation by the host institution of the successful execution of your mission

A letter of confirmation has already been sent directly in a separate email by Prof. Weisz.

Other comments

I would like to thank TINNET for the possibility to perform this very interesting and enlightening short term scientific mission.

References:

Congedo, M., John, R. E., De Ridder, D., & Prichep, L. (2010). Group independent component analysis of resting state EEG in large normative samples. International Journal of Psychophysiology, 78(2), 89-99.

Dohrmann, K., Elbert, T., Schlee, W., & Weisz, N. (2007). Tuning the tinnitus percept by modification of synchronous brain activity. *Restorative Neurology and Neuroscience*, *25*(3-4), 371–378.

Hartmann, T., Lorenz, I., Müller, N., Langguth, B., & Weisz, N. (2013). The effects of neurofeedback on oscillatory processes related to tinnitus. *Brain Topography*, *27*(1), 149-157.

Hartmann, T., Schulz, H., & Weisz, N. (2011). Probing of brain states in real-time: introducing the ConSole environment. Frontiers in Psychology, 2.

Kopřivová, J., Congedo, M., Raszka, M., Praško, J., Brunovský, M., & Horáček, J. (2013). Prediction of treatment response and the effect of independent component neurofeedback in obsessive-compulsive disorder: a randomized, sham-controlled, double-blind study. Neuropsychobiology, 67(4), 210-223.

Lorenz, I., Müller, N., Schlee, W., Hartmann, T., & Weisz, N. (2009). Loss of alpha power is related to increased gamma synchronization—A marker of reduced inhibition in tinnitus? *Neuroscience Letters*, *453*(3), 225–228.

Moazami-Goudarzi, M., Michels, L., Weisz, N., & Jeanmonod, D. (2010). Temporo-insular enhancement of EEG low and high frequencies in patients with chronic tinnitus. *BMC Neuroscience*, *11*(1), 40.

Pascual-Marqui, R. D. (2002). Standardized low-resolution brain electromagnetic tomography (sLORETA): technical details. *Methods and Findings in Experimental and Clinical Pharmacology*, *24*, 5–12.

Weisz, N., Dohrmann, K., & Elbert, T. (2007a). The relevance of spontaneous activity for the coding of the tinnitus sensation. *Progress in Brain Research*, *166*, 61-70.

Weisz, N., Moratti, S., Meinzer, M., Dohrmann, K., & Elbert, T. (2005). Tinnitus perception and distress is related to abnormal spontaneous brain activity as measured by magnetoencephalography. *PLOS Medicine*, *2*(6), e153.

Weisz, N., Müller, S., Schlee, W., Dohrmann, K., Hartmann, T., & Elbert, T. (2007b). The Neural Code of Auditory Phantom Perception. *Journal of Neuroscience*, *27*(6), 1479–1484.