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COST
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BM1306: Better Understanding of the Heterogeneity of Tinnitus to Improve and Develop New Treatments (TINNET)

Short scientific report for the STSM "detecting structural changes in tinnitus subtypes", BM1306_22009

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To whom it may concern

The purpose of the STSM was to apply and share the guest's knowledge about the FreeSurfer (FS) neuroanatomical software suite to detect structural changes in tinnitus subtypes. FS is deemed to generate a more differentiated picture of neuroanatomical states and traits as independent parameters of cortical grey matter are subject to analysis (e.g., changes in volume explained by cortical surface area and/or thickness) in contrast to traditional volumetric approaches like voxel-based morphometry (VBM). Within this framework, it is proposed that static (possibly genetic) and dynamic (neuroplastic) alterations in cortical grey matter tracked by the manifold of FS parameters could be able to identify tinnitus subtypes in general or more specifically detect changes within different subtypes.

As laid down in the detailed working plan in the application process, the actual data set for analysis was chosen within the first week. The choice fell on two longitudinal MRI data sets studying the effects of a transcranial magnetic stimulation (TMS) therapy of tinnitus patients. One of these data sets has recently been published by Lehner and colleagues (2014) and was the first to be analyzed. The respective measures and actual scripts were then generated for the respective neuroanatomical reconstruction pipeline to be run on the cluster computer.
This encompassed a lot of technical preparation and issues on the site as FS only runs on UNIX-based systems as well as is in need of considerable computing power not inherent to casual desktop systems. Although considerable efforts in preparation from the host and guest were deployed to that end beforehand the actual STSM, most of the actual technical proceedings could only be achieved on site in tight personal communication with the IT department and cluster computing specialist of the University of Regensburg. Limited by the available resources of the cluster computer and the demands of the costly calculations of

the longitudinal MRI study brain scans (roughly 5-7 times more computing power needed per subject compared to a cross-sectional neuroanatomical FS analysis), the first data set was being calculated on the cluster computer starting from Wednesday. As the newly developed longitudinal pipeline (Reuter et al., 2012) requires three instead of one cortical reconstruction computing step and one should evaluate the results between the steps, any other planned work efforts were subprioritized and focus was set to get to the stage of statistical analysis of the first data-set as quickly as possible. The computing time could even be reduced for some days due to the gratitude of the responsible operator of the cluster. After receiving and evaluating the data of the third and final iteration, the statistical analysis was immediately begun with while the second data set was transferred to the cluster and computed in parallel.

Table 2: Overview over all VBM analyses.

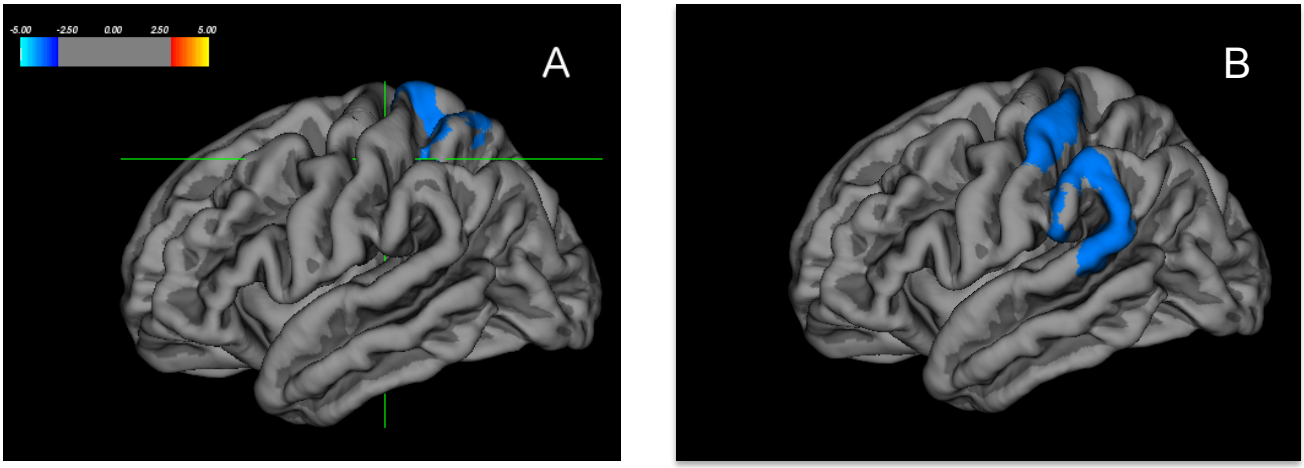
Research question	Statistics		
	$n = 41$ (3 scans)	$n = 36$ (2 scans)	$n = 77$ (whole group 2 scans)
(1) Grey matter changes after rTMS?	Flexible factorial models with factors subject + time		
	Time points: baseline, day 12, day 90	Time points: baseline, day 12	Time points: baseline, day 12
(2) Correlation between grey matter changes and clinical outcome parameters?	Correlation of difference in the TQ/loudness rating with difference images		
	Time difference: day 12–baseline day 90–baseline	Time difference: day 12–baseline	Time difference: day 12–baseline
(3) Grey matter as predictor for treatment response?	Correlation of difference in the TQ with baseline images		

The data analysis stuck to the original design of Lehner et al. (2014), see Table 2 above. The main contrast was the (FS: percentual) change in cortical grey matter in a whole-brain analysis between the pre-treatment MRI scan and the post-treatment scan immediately run after the last TMS treatment. This time interval was measured in all 77 participants which makes it the most interesting contrast also in combination with an expected clear effect, that is change in grey matter, at the time point right after the last treatment. The main results are shown in Figure 1. The results were corrected for multiple comparisons applying monte-carlo null-z simulation. As in the original VBM analysis, only clusters with cluster-wise p-value smaller than 0.001 are depicted.

In contrast to the VBM finding of reduced grey matter volume of clusters with peaks in bilateral inferior frontal gyri, the FS re-analysis was not able to replicate it and produced a reduction in volume in left postcentral regions (Panel A), which seems to be partly explained by a “concurrent” reduction in cortical surface area (Panel B). While both analyses (VBM and FS), cautiously put, failed to produce results in line with the hypothesis of the investigators, that is an increase in cortical grey matter in the targeted area of the TMS intervention (i.e., left primary auditory cortex), the second resulting cluster with a peak in the left supramarginal area reaching to the left posterior superior temporal gyrus is at least neighboring the stimulated area and possibly could show related effects with respect to the extent and spread of the applied magnetic field. Nevertheless, again considering the inhomogeneous results between the analysis methods (i.e., VBM vs. FS) as well as a general scarcity of respective research, the results are hard to interpret as the resulting clusters of cortical volume and surface area are unspecific to tinnitus or even possibly completely unrelated to the intervention

and/or outcome. The use of a respective control group certainly could shatter more decisive light on actual “real” effects.
At this point it is worth mentioning that all other models of the original analysis (see Table 2 above) were also performed (producing an output six times larger than VBM as we looked at 3 parameters (volume, area, thickness) in both cerebral hemispheres). The correlations with the outcome or responding-relevant measures of the difference in tinnitus questionnaire (TQ) score or the loudness change with the baseline grey matter data were also performed but did not produce results interpretable in theory or the findings within the analysis of the actual data set. Consolingly, the loudness change-grey matter correlation of the FS analysis did spawn a cluster at the location of the simple pre-post contrast of the VBM analysis, namely in left inferior gyrus (data not shown). This finding should not be overestimated given the generally heterogeneous results as well as the weak theoretical support.
To conclude this short summary of the results, which were evaluated in a discussion with Dr. Martin Schecklmann and PD. Dr. Berthold Langguth towards a feasible publication, it is suitable to run ROI analyses of the targeted/theorized areas (i.e., primary auditory cortex) with both methods and possibly both data sets. Support for this idea is given by the fact that the pre-post analysis of one subgroup (n=41) did actually produce an increase in cortical surface area in left posterior/medial Heschl’s gyrus and insula in line with the hypothesis (data not shown). Yet the achieved statistical power is not as high as in the main finding, nevertheless it is comparable to the reported clusters in table 3 of the original VBM publication.
Summarizing and evaluating the analysis method- and result-wise a clear heterogeneity of the data as well as uncertainty in its interpretation has to be stated. This is by far not true in the comparison of cross-sectional data between FS and VBM as the results are comparable in site and statistical extent while FS is contributing a differentiated picture of cortical grey matter volume alterations alongside the parameters of area and thickness (publication in prep). In the case of the longitudinal analysis at hand, also in regards to the proposed possible subtypization through area and thickness as proposed in the application documents, this replicating and complementary aspect of the parallel use of the methods is hardly conceivable. Thickness, which was expected to be the marker of short-term neuroplasticity, did not yield any significant results. Volume changes were rather explained by area alterations as seen in the main results (see table 2 and figure 1). It has to be mentioned though that short-term plasticity elicited by morphometry after neuromodulatory interventions of any kind are scarce and that plasticity associated with cortical thickness is better understood in the context of pathologies and aging.

Figure 1



As quickly introduced before, a publication of the data with respective whole-brain and ROI analyses is envisioned with the host institution. Within this publication a special focus on methodological issues and interpretational limitations would play a central role. The paper drafting is planned for March this year.
Furthermore, a continuing collaboration with the host regarding parallel use of VBM and FS was established where the guest will further remotely manage FS analyses while continuing the knowledge transfer. Beyond that, the use of the Trackyourtinnitus mobile application developed by Dr. Winfried Schlee is actually being integrated into a starting tinnitus study in Zurich. As the guest has some background in sound design and actually is planning a respective study with tinnitus sufferers, he got invited by Dr. Schlee to a meeting in auditory stimulation meeting in Munich in the coming October. Concluding this section, another STSM with either auditory stimulation or EEG projects has been proposed.
Concerning general involvement in TINNET/COST Action BM1306, the guest now is a member of the working groups “Database/Subtyping “ (WG2) and “Neuroimaging” (WG3).

To conclude this report, it must be mentioned that initial detailed work plan of the application could not be fully fulfilled when it comes to the first week pre-analyses and actual subtyping efforts/hypotheses. Presciently though it was stated in the work plan that the planned procedure is heavily dependent on the chosen data and analysis. Nevertheless, the analysis of both data sets was achieved within the actual STSM.
I am very thankful for the generous opportunity and the great exchange with the host institute. The inspiring and very professional environment will certainly leave its footprint in the daily work of my doctorate in tinnitus research.

References:

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