Resumé Master Thesis

The research for my master thesis was accomplished in the research group of Prof. Jessica Freiherr at the department of Psychiatry and Psychotherapy, University Hospital, FAU Erlangen-Nürnberg. The initial motivation for this project was to build upon former work of the research group, in which the neural perception of olfactory-trigeminal odor mixtures was examined in behavioral and fMRI studies. The main goal of those studies was to evaluate the potential of eucalyptol to mask the sensation of ammonia. Both stimuli activate both the olfactory and the trigeminal system, as it becomes apparent in the cooling effect of eucalyptol or the irritating effect of ammonia in the nose. The brain activity of healthy participants was measured in a 3T MRI scanner, while Participants were presented ammonia, eucalyptol, a mixture of both or an odorless baseline. For each stimulus, the participants had to rate the intensity of the eucalyptol and ammonia sensation, of the overall stimulus, and the pleasantness of the overall stimulus, all while their respiration was measured. While it could be shown that eucalyptol can mask the olfactory but not the trigeminal sensation of ammonia, there were also new questions raised by that study. One question concerns an unexpected activation pattern: Around 30 s after stimulus presentation, a second activation peak additional to the usual first peak was visible (Fig. 1). The aim of my master project was to investigate this question from multiple different perspectives. It can therefore be seen as a continuation of the previous work of the research group and at the same time as a preliminary study for parts of my doctorate project. The data available for our project consisted of study population data like physical features (BMI), psychometric questionnaires (BDI, MOCA) and smelling capability tests (MONEX-40), of the neuroimaging data, respiration data, and of the

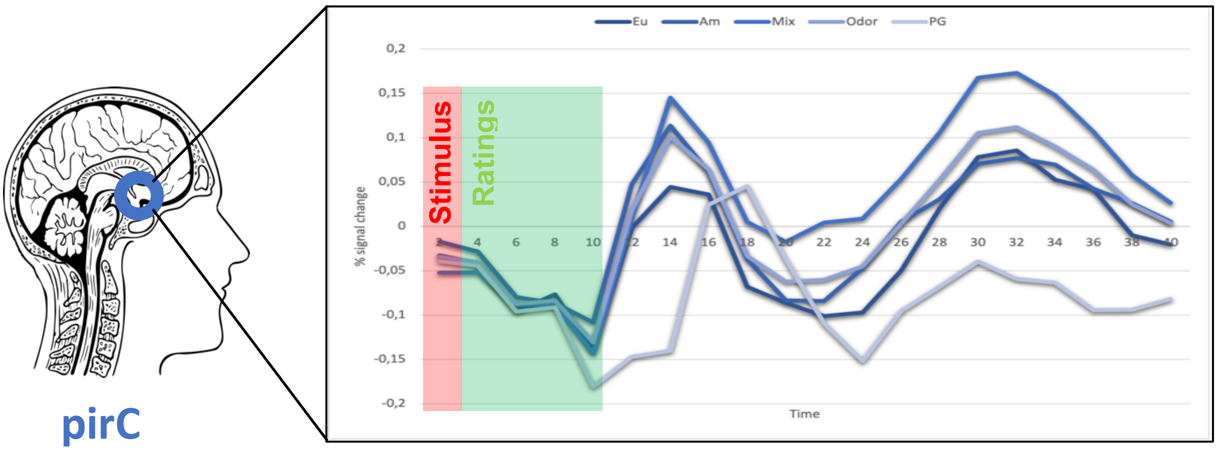

Figure 1: Activation time course in the piriform cortex. After the typical peak of the hemodynamic response function after 14s, a second, unexpected peak is visible 30s after stimulus presentation.

answers to the behavioral rating tasks (rating intensity ammonia/eucalyptol/overall, rating pleasantness overall). We first applied the standard processing pipeline using SPM and MATLAB. For the subject analysis, we included both the stimulus presentations and the rating tasks as “events”. Our idea was to treat the rating tasks as singular events, the resulting brain activation should therefore specifically show the regions activated in response to the rating task, not the stimulus itself. With this, we hoped to find a neural correlate of the second activation peak. For the group analysis we applied a flexible factorial design with a subject factor and a “condition” factor with levels representing the different stimuli and rating tasks. When contrasting the statistical parametric maps of each rating tasks to the activation after stimulus presentation, and comparing between the different rating tasks, we found that especially after the task to rate the ammonia component, the hippocampal region was activated significantly higher. This might hint towards memory effects which are in place specifically after the participants get asked to rate the ammonia sensation, possibly because the brain evokes the memory of this painful and dangerously perceived stimulus in order to avoid a repeated exposition. To further access this question, we did a time series analysis in several regions of interest (piriform cortex, orbifrontal cortex, insula, amygdala, hippocampus, cingulate gyrus, and others). We found that the second activation peak was present in all regions involved in olfactory processing. Next, we looked specifically at the activation in response to the specific rating tasks. We therefore got one activation curve for each rating task per brain region. Our idea was to see which activation related to the rating tasks shows the highest correlation with the second peak in that brain region. We found that in most regions, the signal change related to the task to rate the pleasantness of the total stimulus showed the highest correlation, indicating that this rating task might be the cause of the second peak. We further expanded this approach to the respiration curves and found that such a positive correlation was also visible between amplitude and prominence of the respiration and the second peak activation pattern. This implies that the respiration also plays a role in evoking this second peak. Conclusively, these results could indicate that the task to rate the pleasantness leads to a change in respiration, possibly an unconscious second inhale, which might be necessary to increase the amount of odorant molecules in the nose. Both phenomena could be described as different version of a “second stimulus presentation”, meaning that the second activation peak could be the results of memory or respiration related effects that resemble the initial stimulus presentation. To investigate this concept of a “second stimulus presentation", we trained a machine learning model using so called support vector machines (SVMs). With this approach, called multivariate parametric analysis (MVPA), one can create a model that is able to predict which stimulus was presented from the activation patterns visible in a specific brain region. We trained such a model on the patterns after each stimulus. We then applied that model on the patterns related to the respective stimulus pleasantness rating tasks. The model was able to correctly predict the stimulus from the rating task patterns significantly higher than chance (25%) in the case of eucalyptol (40.9%) and ammonia (43.9%).

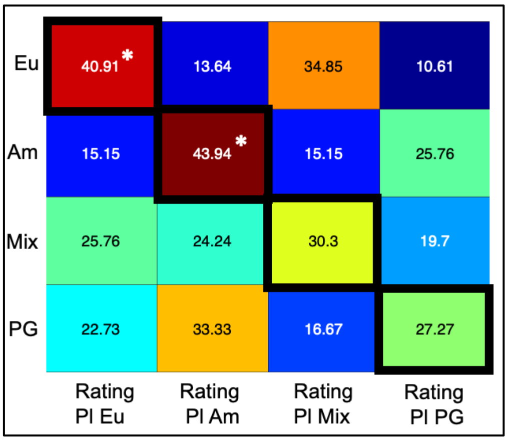

Figure 2: Table showing the prediction accuracy of a SVM model trained on the activation patterns after stimulus presentation (vertical) and applied on the activation patterns after the pleasantness rating tasks of the four stimuli (horizontal). The fields where the predicted stimulus would equal the actual stimulus are highlighted with black bars, the accuracies which show a correct prediction significantly more often than chance are marked with an asterisk (p<0.05).

In other words: The patterns in the brain in response to the question "How pleasant is this stimulus?" seem to be similar to the patterns found after the actual stimulus presentation. This finding supports the thesis of a "second stimulus presentation".

A behavioral study, which will be continued and expanded during my doctorate project, has already started. This study replicates the setup of the initial fMRI experiment on a purely behavioral level. Other than in the initial study, two runs are being conducted, one with and one without the pleasantness rating task. An ethical agreement and all preparations for this part have already been done and first runs have been completed.

Overall, this project offered a methodically multifaceted approach to the question of the unexpected second peak. Using statistical, computational, and behavioral approaches, we narrowed the field of potential origins to the two main hypotheses of memory and respiration effects, summarized under the "second stimulus presentation" thesis. To further develop these first findings, it is indispensable to investigate them using neuroimaging techniques like fMRI or fNIRS. Ultimately, this question could have a huge impact on how future fMRI studies are conducted. If this second peak is present in all fMRI setting, but has just not been seen yet, it's not unlikely that this second activation peak leads to interference with the activation patterns of the next stimulus. This would imply that for future fMRI studies, or at least those using olfactory-trigeminal stimuli, it should be advised to extend the interstimulus interval to at least 30s.