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The effects of spatial resolution and physiological contrast on fMRI patterns

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Chapter 5

Summary & General discussion

The research presented in this thesis contributes to the field of fMRI methodology in cognitive neuroscience both in terms of data acquisition and analysis and unveils the mechanisms underlying sound processing in the human auditory cortex.

5.1 Summary

In **Chapter 2**, we addressed an open debate about multivariate pattern analysis (MVPA) in fMRI research. Although, the use of MVPA in fMRI studies has massively increased in the past decade and sometimes even replaced univariate analysis, little is known about the physical and physiological underpinnings of MVPA in fMRI. Different theories have been proposed and investigated, although using a limited range of experiments (visual tasks and 3T fMRI) and yielding conflicting results. Thus, many questions, such as "What is the source of the signal detected by MVPA decoding?", "What is the optimal spatial resolution of acquisition for fMRI data undergoing MVPA?", and "What is the effect of spatial smoothing on MVPA performances?", are still open to debate. In Chapter 2, we have addressed these questions using ultra-high field (7T) fMRI. The primary research aim was to investigate the effect of spatial resolution and smoothing on decoding of speech content (vowels) and speaker identity from auditory cortical responses. The spatial resolution was varied thanks to a novel approach, in which the complex k-space was first reconstructed from the magnitude and phase images acquired at the highest spatial resolution and then downsampled. In addition, data at each resolution were smoothed using a range of 3D Gaussian kernel sizes.

Decoding of vowel and speaker identity was demonstrated to be feasible at 7T for all spatial resolutions and smoothing kernels tested. The effect of spatial smoothing on decoding performances was similar for vowel and speaker decoding: moderate smoothing improved the decoding accuracies, while large smoothing kernels deteriorated them. The effect of spatial resolution, instead, was different across the two decoding tasks: increasing the spatial resolution yielded significantly higher accuracies for vowel decoding, but not for speaker decoding. These results suggest a distinct spatial arrangement of the neural/neuro-vascular sources underlying vowel and speaker representation and processing in the auditory cortex. Moreover, they indicate the need of empirical studies to investigate the optimal acquisition in view of fMRI MVPA as it was shown to differ among

decoding tasks even when using the same stimuli and decoding from the same brain regions.

To characterize the physiological origin of the multivariate information in fMRI, we ranked active voxels according to their likelihood of containing gray matter (micro-vasculature) or large blood vessels (macro-vasculature). We found that discriminability power is distributed over the continuum of tissue type, with a slightly, but significantly, higher contribution from gray matter than from blood vessel voxels. It is expected that this distinction will be further emphasized in going to higher spatial resolution, further reducing partial volume effects. The complex origin of the BOLD signal and its bias in presence of draining veins makes understanding of the role of tissue types in fMRI MVPA even more complicated. Other fMRI techniques, such as cerebral blood flow (CBF) measured with arterial spin labeling (ASL), for instance, have been demonstrated having higher spatial specificity and closer link to the neural activation than GE-EPI BOLD signal. Moreover, CBF is a quantitative physiological measure with straightforward interpretability. It could be therefore beneficial using CBF to study the physiological underpinnings of MVPA and, more generally, the functional organization of the brain. These considerations motivated our **Chapter 3**, in which we used pseudo-continuous ASL at 3T to study the functional organization of the human auditory cortex. In particular, we aimed at mapping tonotopy and voice selective regions in the human auditory cortex using, for the first time, CBF signal instead of the standardly used BOLD signal. Further, we addressed the unresolved issue of the anatomical and functional delineation of the primary auditory core. Finally, we investigated the tissue specificity of CBF and BOLD signal and the possible venous bias of BOLD-based tonotopy.

CBF-based tonotopy showed two main gradients composing a V-shaped pattern of high-low-high preferred frequency centered on Heschl's gyrus and additional frequency gradients in the surrounding regions. The good agreement with BOLD signal-based tonotopy demonstrated the feasibility of CBF-based tonotopy and provided a reciprocal validation of the CBF- and BOLD signal-based findings. Despite the relatively good agreement between CBF- and BOLD-based voice selective maps, two out of five peaks of voice selectivity did not reach significance for CBF. We attributed the missed detection of some voice selective regions and smoother CBF tonotopic maps to the lower SNR of CBF with respect to the BOLD signal. Importantly, quantitative baseline perfusion maps showed a region of high perfusion centered on Heschl's gyrus and corresponding to the main

high-low-high frequency gradients, co-located to the presumed primary auditory core, usually delineated by anatomical landmarks. These observations suggest baseline CBF as a novel anatomical marker for parcellation of the auditory cortex. Finally, we assessed the tissue specificity of CBF and BOLD signal using vein masks computed from SWI images. We found a higher specificity to microvasculature for CBF signal, whilst a venous bias for the BOLD signal. However, our hypothesis that such venous bias of the BOLD signal could be the cause of local mismatches between CBF- and BOLD-based tonotopy did not find significant evidence in the data.

Taking all results of this study together, we showed that both baseline and stimulus-induced CBF is an alternative fMRI approach to the standard BOLD signal to study auditory processing and delineate the functional organization of the human auditory cortex. In future studies, the combination of CBF signal and MVPA analysis could help to further explore the functional auditory cortex and the underpinnings of MVPA fMRI itself.

In Chapter 3, we described the benefits and limitations of ASL fMRI. The latter were primarily identified in the low SNR of CBF signal and motivated the project presented in **Chapter 4**, where different ASL implementations were compared in view of their utilization to simultaneously acquire CBF and BOLD signal in fMRI studies. To that end, the chosen ASL implementations had to fulfill some criteria, such as short TR, TE(s) adequate to both CBF and BOLD acquisition (therefore also no background suppression), (relatively) high spatial resolution, and sufficient brain coverage. We performed one resting-state and one activation study, in which we compared different ASL MRI approaches (FAIR QUIPSS II, PICORE Q2TIPS (only for the resting-state experiment), and pCASL at 3T and FAIR QUIPSS II at 7T). In the resting-state experiment, the voxel size was fixed at 3.0 mm isotropic and no parallel imaging was used. In the activation experiment (consisting of visual stimulation presented in blocks), the acquisitions were repeated at four different resolutions (1.5, 2.0, 2.5, and 3.0 mm in-plane resolution for 3.0 mm slice thickness) and GRAPPA 3 was used. For comparison purposes, one run was acquired with a pCASL implementation tuned accordingly to the recommendations of the ASL white paper (Alsop et al., 2015).

Our results showed that for low spatial resolution (3.0 mm isotropic) and no parallel imaging, 3T FAIR and pCASL yield the highest tSNR and perfusion SNR and are therefore preferable over 3T PQ2T and 7T FAIR. However, increasing spatial resolution and using parallel imaging (GRAPPA) favor the use of 7T FAIR

above all and 3T pCASL above 3T FAIR. Such choice is indicated by tSNR, perfusion SNR and functional sensitivity (assessed as amount of significant activation detected in response to the visual stimuli) measures.

Concerning the quantification of baseline perfusion, 3T ASL schemes resulted in quantitative values in good agreement with those obtained with the "ASL white paper" protocol (chosen as gold standard), providing therefore a validation of the 3T ASL protocols used in our studies. 7T FAIR yielded a significantly lower mean GM perfusion value than 3T ASL schemes. We attributed such discrepancy to differences in the apparent transverse relaxation time of blood and tissue, which are negligible at 3T but not at 7T, and to decreased labelling efficiency at the 7T due to field inhomogeneities.

These results lead to the recommendation to use 3T FAIR or pCASL for studies using low spatial resolution (3.0 mm isotropic and lower) and no parallel imaging, while 7T FAIR for high-resolution and/or studies employing parallel imaging.

5.2 Conclusions and outlook

In conclusion, from a methodological point of view, the studies included in this thesis shed further light on the mechanisms underlying MVPA fMRI, the optimal acquisition and preprocessing of fMRI data undergoing MVPA analysis, the use of stimulus-induced CBF to investigate the functional organization of the brain, the use of baseline CBF to investigate the parcellation of the cortex, and the recommended ASL implementation to employ to achieve these aims. From a neuroscientific point of view, this thesis provides new insights on auditory cortical processing of basic acoustic features (frequency) as well as on the cortical representation of speech content (vowel) and speaker identity. Furthermore, this thesis put forward a novel, simple approach to delineate the primary auditory core.

In the following paragraph, we will comment on specific aspects of the studies, as summarized above, and take the freedom of speculating about possible implications and/or outlooks.

In Chapter 2, we observed different hemodynamic response function (HRF) shapes in different regions of the auditory cortex. For this reason, instead of using a fixed predictor model, we built a range of HRF models with different time-to-peak shifts and chose for each voxel the HRF shift which gave the best fit to

the mean over all trials. This approach represents a first attempt to take into account such HRF variability, however, the flexibility of the models used was quite limited. A more flexible model of HRF shape customizable for each voxel (or brain regions) could result in a more accurate fit of each trial (both training and testing trials) and therefore in an improvement of decoding accuracies.

A range of adaptive models of HRF have been proposed (e.g., Friston et al., 1998; Dale, 1999; Glover, 1999; Woolrich et al., 2004; Lindquist and Wager, 2007), which offer different degrees of flexibility. For instance, in a recent study, Pedregosa et al. (2015) implemented a voxel-by-voxel estimation with a three basis functions model and showed its higher statistical power with respect to other competing models in both encoding and decoding experiments.

Nevertheless, HRF fitting is generally not employed in decoding studies as flexibility of the HRF model comes at the cost of risk of overfitting and resulting in not physiologically plausible hemodynamic shapes, especially in case of low SNR voxels. Therefore, using β-values (or t-values) provided by fitting with "too" flexible models as features of the MVPA algorithm could be, on the contrary, deleterious for the decoding. Moreover, including HRF modelling within MVPA importantly increases its complexity and computational costs as flexible models requires fitting several parameters (and not only one as for GLM with a fixed HRF model). One approach to take into account HRF variability across voxels could be to: 1) estimate the HRF voxel-wise from the training data or an independent experimental paradigm (e.g., using flexible basis functions or a finite response model), 2) describe each voxel's response with a single feature (e.g., its peak amplitude), and then 3) apply the voxel-specific HRFs to derive an estimate of features from the test data (see e.g., Kay et al., 2008a,b; Santoro et al., 2014). Alternatively, one could use multiple features for each voxel including all parameters describing the HRF estimate of that voxel. The rationale behind this approach is that, if the HRF shape itself (and not only its amplitude) carries information about the representation of a certain stimulus, including its parameterization should be informative for the algorithm and beneficial for the decoding. However, combining multiple features in a machine learning algorithm is not trivial and different strategies are possible, among which: the multiple voxel-wise features associated with the different HRF parameters could be concatenated to form a higher dimensional space, or decoding could be performed using multiple kernels corresponding to the multiple features and later recombined.

All different approaches offer advantages, challenges and limitations, thus

theoretical and empirical studies are required in order to develop and evaluate both aforementioned and new approaches to best account for HRF variability in decoding fMRI.

In Chapter 2, we also investigated the tissue specificity of the discriminability power and found that both micro- and macro-vasculature contributed to it. Oversimplifying the issue for a moment, one could think that if the hypothesis of voxel biased sampling is correct, the multivariate information should come from the micro-vasculature (GM), while, if the biased draining region hypothesis is correct, the information should come from the macro-vasculature (draining veins). Our study was conducted with GE-EPI, hence the fMRI signal originated both from micro- and macro-vasculature. As explained in Chapter 3, CBF measured by ASL represents an alternative technique to BOLD fMRI and has the advantage of being localized to the micro-vasculature. Performing a decoding study with ASL could, therefore, allow testing of the two hypotheses and disentangle the origin of the multivariate information. The ability of ASL to simultaneously acquire both CBF and BOLD signal would represent a major strength to this aim, however, under the assumption that both signals had comparable (or at least "enough") SNR. Chapter 3 and 4, unfortunately, speak against the fulfilling of such a requirement by current ASL techniques as the current major drawback of CBF signal is indeed its low SNR (compared to the BOLD signal). In view of future improvements, 7T ASL seems to be the method of choice to this aim because it was found to be the ASL implementation with higher SNR in case of high resolution imaging. High resolution would be indeed another necessary requirement in such project in order to avoid biases due to partial volume effects. Newly introduced 3D ASL acquisitions, such as 3D RARE Stack-Of-Spirals (Ye et al., 2000; Dai et al., 2008; Xu et al., 2010) or 3D GRASE (Gunther et al., 2005), seem also promising in terms of CBF SNR improvement (Vidorreta et al., 2013) and should also be evaluated in further studies.

Baseline perfusion was demonstrated informative on the delineation between primary and secondary areas in auditory cortex (in Chapter 3) and in visual cortex (Weber et al., 2008). Cortical parcellation has been object of study since Brodmann's work (Brodmann, 1909) and has been conducted under the assumption of a close relationship between anatomical and functional properties. Thus, cytoarchitectonics became the leading technique to define structural and functional organization of the brain. Next to it, other techniques such as myeloarchitecture and receptoarchitecture have been used (Smith, 1907; Vogt and Vogt, 1919;

Zilles et al., 2002). With the advent of neuroimaging, cortical parcellation based on myeloarchitecture and (functional) connectivity has gained increasing attention also thanks to their *in vivo* potential (Clark et al., 1992; Barbier et al., 2002; Sigalovsky et al., 2006; Kim et al., 2009; De Martino et al., 2015). Although all mentioned techniques should concur to describe the same functional specialization of cortical areas, the relationship and agreement between the resulting parcellations is still unclear (Cloutman and Lambon Ralph, 2012). Instead of comparing parcellations based on different techniques, recent efforts have been focused on combining them into a multi-modal parcellation approach. In Glasser et al. (2016), a multi-modal approach using both structural (namely, T_1- and T_2-weighted images delivering myelin content and cortical thickness information) and functional (task and resting-state modality) images was combined with machine learning techniques to enable area delineation and thus proving the advantages of integrating information from different modalities. So far, to the best of our knowledge, no multi-modal parcellation method has included perfusion data. However, our findings in Chapter 3 and given the physiological link of CBF with micro-vasculature and metabolic demand of the tissue (Weber et al., 2008), we believe that perfusion signal represents a quite unique marker of both anatomical and functional properties and that it could add relevant complementary information for cortical parcellation.

Multi-modality neuroimaging and machine learning algorithms appear to be two key factors for future developments in the cognitive neuroscience field. A first step in this direction was taken for example by Glasser et al. (2016) who, on the basis of a rich multi-modal database provided by the Human Connectome Project, built an areal classifier able to semi-automatically delineate and identify cortical areas in new individual subjects, even with atypical parcellation. This study also highlights another challenge of the current neuroscientific research: moving from a group-averaging approach to an individual focus and personalized investigation (Dubois and Adolphs, 2016). To this aim, quantitative, robust, and reproducible methods will likely play a major role and open the way for translational applications in clinical and pharmacological research at the single-patient level (Pike, 2012).

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