# Additional information about Glasser52

## Why a new parcellation?

### The ‘default’ parcellation

The parcellation (Colclough et al., 2015, 2016) used by most of the current HMM-papers use (Higgins et al., 2021; Quinn et al., 2018; Sitnikova et al., 2018; Vidaurre et al., 2018, p. 201) , divides the cortex into 39 weighted parcels. Single parcels were inferred from a group-spatial-ICA decomposition of the fMRI scans of the first 200 subjects of the Human Connectome Project (Van Essen et al., 2013). The generation of parcels based on functional activity has the advantage to cluster brain regions based on their functional specificity (Colclough et al., 2015). This makes the parcellation more suitable for analyses on functional activity, as recorded by MEG, compared to parcellations based on anatomical or histological features of the cortex.

### Potential shortcomings

The procedure described above results in two potential shortcomings.

1. Functionally inferred parcels are difficult to link to anatomical labels which reduces interpretability of obtained findings in the context of other studies that use different parcellations.
2. Dividing the cortex into 39 parcels results in relatively coarse parcels which may conceal specific areas with distinct functional specificity. I.e., comparisons between activity in the supplementary motor area and motor are not possible because of large parcels.

## Specific requirements of a parcellation for HMM-Analyses in MEG data

The pre-processing pipeline recommended to apply before running HMM-analyses (Quinn et al., 2018) contains several steps (Maxfiltering and ICA artefact removal or Signal-Space projection) that first separate the data into subcomponents and then keep only a subset of components predominantly containing the signal. Each of these steps reduces the dimensionality or rank of the data to ~60 (Quinn et al., 2018). This sets an upper limit for the maximal number of parcels that the MEG data can be parcellated into if spatial leakage correction is applied to the data.

Parcellating the data into more than ~60 parcels will result in rank deficiency which means that neural activity of some parcels is a linear combination of the other parcels and thus, does not arise from a separate source. The last step of the pre-processing, i.e., spatial leakage correction, is applied to reduce the blurring of sources into its neighbouring regions by orthogonalizing parcel time courses (Colclough et al., 2015). Crucially, the orthogonalization process requires full-rank data because the orthogonalization of parcel time courses that can be expressed as a linear combination of other parcel time courses is not possible. This means that in our case a parcellation should have less the ~60 parcels.

Importantly, the rank of the pre-processed data is ~60 which means that it is possible to extract signals for more than 39 parcels from the MEG data which would enable for a higher spatial resolution of our analyses.

## The Goal

We are aiming to create new parcellation with 52 parcels that can be linked to anatomical labels and is suitable for analyses of functional MEG-activity

# How the parcellation was created

To address the aforementioned issues we are planning created a new parcellation with 52 parcels based on the Human Connectome Project Multimodal Parcellation (HCP-MMP) atlas (Glasser et al., 2016). The new parcellation was created based on a procedure suggested by Tait et al. (2021). The first two steps comprising the calculation of region importance and data-driven inference suggesting which regions to split were performed identical to Tait et al. (2021). The implementation of the recommended splits, however, deviated a bit from the described procedure because we were aiming to create an atlas with a much smaller number of parcels (52 vs. 230 parcels).

## Human Connectome Project Multimodal Parcellation (Glasser et al., 2016)

The HCP-MMP parcellation divides the cortex into 180 parcels per hemisphere using an objective semi-automated neuroanatomical approach informed by multimodal magnetic resonance images (MRI) information. Multimodal MRI information was retrieved from areal properties of architecture (T1w/T2w myelin and cortical thickness maps), function (task-fMRI response to 7 tasks), functional connectivity (pairwise Person correlation between resting state time series of Gray ordinates), and intra-area topographic organisation inferred from the HCP. The multimodal nature of the considered information is supposed to result in better neuroanatomical precision and functional segregation of the parcels. In the Supplementary Information the authors further group the 180 cortical areas into 22 regions based on observability on the inflated cortical surface from a single viewing perspective and shared architectural, task-MRI and functional connectivity profiles (see Supplementary Neuroanatomical Results of Glasser et al. (2016)).

## Tait approach

Based on the 22 regions in the HCP-MMP atlas we are planning to create a new parcellation with 52 parcels with equal influence on the MEG sensor signal according to the procedure suggested by Tait et al. (2021). The underlying idea of this procedure is to calculate the influence of each of the 22 regions on the MEG sensor signal and then merge and divide regions so that 52 parcels with similar influence on the MEG sensor signal are obtained. The merging and dividing process is informed by the neuroanatomical information provided by Glasser et al. (2016). **In summary, this approach allows to start from an anatomical parcellation and to adapt it to the functional signal that was measured with MEG. Thus, it enables for a good compromise between solely anatomical or solely functional derived parcellations.**

### Calculation of Region Importance

The importance (or influence on the MEG sensor signal) of each of the 22 regions specified by Glasser et al. (2016) was calculated based on the individual lead fields obtained from the source reconstruction pre-processing step. The influence of a single voxel on a subject’s MEG sensor signal was calculated as the sum of the Euclidean norms of the three columns of the voxel’s lead file matrix. To establish the subject’s region importance values, the voxel importance of all voxels allocated to the respective region were summed. This procedure was repeated for each subject separately. The overall region importance was calculated as the average across region importance values of all subjects.

The optimal number of parcels per region was calculated by normalising each regions importance to the overall importance across parcels and multiplying the obtained relative region importance values with the desired number of parcels (50). Each of the resulting values indicated the optimal number of parcels per region for a desired total number of 50 parcels. As a consequence of this procedure, regions with high importance are divided into a larger number of parcels whereas less important parcels are not split at all or even recommended to be merge with other regions.

Opposing to Tait et al. (2021), we created in a parcellation with a smaller number of parcels (50 vs. 230 parcels) which resulted for two regions with low importance in a recommended parcel number of zero. In both of these cases, we broke with the rational of Tait et al. (2021) to maintain coverage of regions specified by Glasser et al. (2016) and merged regions based on spatial and functional proximity. At the same time this allowed to split regions with very high importance into more parcels which in turn resulted in a larger spatial resolution in regions that have a strong influence on the MEG sensor signal. The splitting of regions was preformed based on the information on single ROIs within a region provided in the Supplementary Information of Glasser et al. (2016). (We mainly focused on functional connectivity and task-activation of ROIs).

## Merging of parcels in OSL

A MNI-space version of the HCP-MMP atlas with a voxel resolution of 2x2x2 mm was downloaded from <https://github.com/neurodata/neuroparc> (Lawrence et al., 2021) and transformed into a 4d matrix (x-coordinates, y-coordinates ,z-coordinates ,ROI-number) containing a binary MNI-space mask for each of the parcels in the atlas. According to the results of the regional importance calculation, ROIs of the HCP-MMP parcellation were merged to obtain a reduced HCP-MMP version with 50 parcels. Since the primary motor and sensory cortex of the HCP-MMP parcellation are represented just as a long ROI spanning from superior to inferior and previous research implicated that the superior and medial motor cortex might be involved in functionally distinct processes in Parkinson’s Disease (Oswal et al., 2016) we decided to subdivide the obtained sensorimotor parcels in the reduced HCP-MMP version. Both parcels were divided into 2 sub-parcels based on K-means clustering of the voxel coordinates (as implemented in OSL). The resulting new parcel divided the primary sensorimotor cortices into a superior and inferior part. Thus, at the end of the merging procedure we ended up with a reduced version of the HCP-MMP atlas with 52 parcels.

To bring the obtained parcellation in the same format as the currently used parcellation for HMM and OSL-Analyses (Colclough et al., 2015, 2016) we resampled the parcellation from a 2x2x2mm voxel size to a 8x8x8mm voxel size with the FSL flirt function (Jenkinson et al., 2002) using the trilinear interpolation option and binarized it afterwards.

## Sanity checks

For each parcel of the new reduced HCP-MMP parcellation its influence on the MEG sensor signal was calculated according to the described procedure above to check whether the influence on the MEG sensor signal is uniformly distributed across parcels.

To further check whether parcellating the data into the new parcellation results in rank deficiency and problems during leakage correction we applied leakage correction to the parcellated data and calculated group-average power spectra for each parcel from the data with leakage correction applied and without leakage correction applied. This procedure also allowed to check whether leakage results in unexpected power spectra which might occur when a region picking up signal from the same source is split into two parcels that then reflect activity from the same source. The same procedure was also repeated for a subject with especially noisy data and 5 removed ICA components during ICA artefact removal.

# Results

## Description of the Merging Process

Relative parcel importance values for each of the regions can be seen in Figure 1. Not surprisingly, the Primary Visual Cortex (V1) (Region 1) showed the lowest importance which is likely due to the reason that this region consists of a single ROI whereas all the other regions comprise several ROIs. Based on spatial proximity and similar functioning, this region was merged with the Early Visual Cortex region (Region 2). The Posterior Opercular Cortex also showed a very low importance and was merged with the Insular and Frontal Opercular cortex (Region 12) because these regions are often grouped together and assumed to be involved in gustatory functioning as well as primary somatosensory and motor functioning (Martin et al., 2012). Opposing to this the Paracentral Lobular and Mod Cingulate Cortex (Region 7) had a high importance and was divided into a Supplementary Motor Area Parcel and a Cingulate Motor Cortex and subdivision of Area 5 parcel. Similarly, the Superior Parietal Cortex (Region 16) was split into a Medial Bank of the Intraparietal Sulcus parcel and a Superior Medial Parietal Cortex parcel. The Dorsolateral-Prefrontal Cortex (DLPFC) (Region 22) was split into an inferior DLPFC parcel and a superior DLPFC parcel. The Inferior Parietal Cortex (Region 18) was the region with the highest influence on the MEG sensor signal and therefor, was split into three parcels: Inferior Parietal Cortex Task-Positive Network, Inferior Parietal Cortex Task-Negative Network, and Intraparietal Sulcus + PGP. A table documenting the merging process can be found at the end of this document.

*Chart, bar chart

Description automatically generated*

Figure 1.Normalised importance values for regions specified by Glasser et al. (2016). Yellow bars are suggested to be split according to the algorithm suggested by Tate et al. (2021). Region 1 and 2 and region 9 and 12 (orange bars) were decided to be merged because of the low importance values of region 1 and region 9.

## Sanity Checks

Importance values for each parcel in the new parcellation were calculated to check whether the splitting procedure yielded parcels with very low influence of the MEG sensor signal (Figure 2). The importance of all parcels created by splitting was within the range of importance values of parcels that were not split or merged. Importantly, even the motor split that we decided to conduct based on theoretical reasons and not based on the importance analysis, yielded parcels with importance values within the range of the other parcels.

Chart, bar chart

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Figure 2. Relative Importance Values of all parcels in the new parcellation. Orange bars mark importance of parcels that were created by merging Glasser et al. (2016) regions, blue bars represent parcels created by motor split, and yellow pars indicate parcels created by splitting regions.

A collage of images of the brain

Description automatically generated

Figure 3. An overview of the newly created parcellation from different perspectives. Each parcel is represented by a different shade of red or blue. B All motor parcels overlayed on brain template.

To further check whether parcellating the MEG data into the new parcellation results in rank deficiency and consequently to errors during the symmetrical leakage correction (Colclough et al., 2015) we calculated a group-average power spectrum selected parcels. No erros occurred during leakage correction and the overall shape of power spectra looked similar between power spectra calculated on data with leakage correction applied and data without leakage correction applied (Figure 5). A similar pattern was observed when the analysis was repeated on a single subject with noisy data.

Line chart

Description automatically generated with medium confidence

Figure 4. Group-average power spectra of parcels within broader brain regions. Plots on the left side show results on data without leakage correction applied and plots on the right-side show results after applying leakage correction.

# Procedure

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| --- | --- |
| Get 2x2x2 MNI space HCP parcellation | Downloaded from [neuroparc](https://github.com/neurodata/neuroparc). (<https://doi.org/10.1038/s41597-021-00849-3>) |
| Bring Parcellation in OSL shape | Built 4d parcellation matrix containing binary mask for MNI coordinates for each parcel stacked along 4th dimension |
| Run Source Reconstruction of MEG data |  |
| Calculate ROI Importance | According to Tait et al., 2021: importance of each voxel (or its influence on the MEG sensors) is calculated as the norm of 3 dipole orientation columns in lead field matrix of respective voxel.  ROI importance is calculated as the sum of the voxel importance of all voxels being allocated to respective ROI. |
| Calculate Cluster Importance | After previous step is repeated for lead field of each subject, ROI importance is averaged across subjects to receive average ROI importance.  Average ROI importance values for ROIs being allocated to a Cluster are summed to calculate Cluster Importance, which is input for the next step. |
| Determination which clusters should be split or merged based on Cluster importance (or influence on signal picked up by MEG sensors) | Cluster Importance Matrix is normalised against overall Importance across all parcels.  Relative cluster importance values are multiplied with aimed parcel number in final parcellation. Results in an estimation of how many of our parcels should be used to represent a cluster based on its importance. |
| Decision on clusters that are not very important, and algorithm suggests allocating zero parcels to. | For 2 parcels (V1, and opercular parietal cortex) the algorithm suggested to use 0 parcels to represent these cluster. Two allow us to get a higher spatial resolution/number of splits in parcels with high importance we decided to merge these clusters to other clusters based on anatomical, and functional considerations. V1 merged to early visual areas, and parietal opercular cortex to frontal opercular cortex. |
| Decision on splitting Clusters into parcels | The algorithm suggested to split 3 Clusters into 2 parcels (Dorsolateral Prefrontal Cortex, Superior Parietal Cortex, and Paracentral Lobular and Mod cingulate Cortex) and one cluster into 3 parcels (Inferior Cingulate Cortex) |
| Merging of parcels and splitting along longitudinal fissure | 180 Glasser parcellation in 2x2x2mm MNI space loaded.  Parcels merged according to results of previous two steps. And split bilateral parcels along longitudinal fissure into unilateral parcels one for each hemisphere. |
| Resampling to 8x8x8mm and binarization. | Resampling of parcellation to reference image 8x8x8 MNI template using [flirt](https://doi.org/10.1006/nimg.2002.1132) with trilinear interpolation. Resulting weighted parcellation binarized by selecting the parcel with the highest value after interpolation |
| Check of New Parcellation | Parcel importance of each parcel in the newly created parcellation were calculated to check whether importance is relatively evenly distributed across parcels.  Secondly, power spectra of motor parcels, occipital, and frontal parcels were calculated for all subjects, and we checked whether signal still contained information after applying leakage correction. |

# References

Colclough, G. L., Brookes, M. J., Smith, S. M., & Woolrich, M. W. (2015). A symmetric multivariate leakage correction for MEG connectomes. *NeuroImage*, *117*, 439–448. https://doi.org/10.1016/j.neuroimage.2015.03.071

Colclough, G. L., Woolrich, M. W., Tewarie, P. K., Brookes, M. J., Quinn, A. J., & Smith, S. M. (2016). How reliable are MEG resting-state connectivity metrics? *NeuroImage*, *138*, 284–293. https://doi.org/10.1016/j.neuroimage.2016.05.070

Glasser, M. F., Coalson, T. S., Robinson, E. C., Hacker, C. D., Harwell, J., Yacoub, E., Ugurbil, K., Andersson, J., Beckmann, C. F., Jenkinson, M., Smith, S. M., & Van Essen, D. C. (2016). A multi-modal parcellation of human cerebral cortex. *Nature*, *536*(7615), 171–178. https://doi.org/10.1038/nature18933

Higgins, C., Liu, Y., Vidaurre, D., Kurth-Nelson, Z., Dolan, R., Behrens, T., & Woolrich, M. (2021). Replay bursts in humans coincide with activation of the default mode and parietal alpha networks. *Neuron*, *109*(5), 882-893.e7. https://doi.org/10.1016/j.neuron.2020.12.007

Jenkinson, M., Bannister, P., Brady, M., & Smith, S. (2002). Improved Optimization for the Robust and Accurate Linear Registration and Motion Correction of Brain Images. *NeuroImage*, *17*(2), 825–841. https://doi.org/10.1006/nimg.2002.1132

Lawrence, R. M., Bridgeford, E. W., Myers, P. E., Arvapalli, G. C., Ramachandran, S. C., Pisner, D. A., Frank, P. F., Lemmer, A. D., Nikolaidis, A., & Vogelstein, J. T. (2021). Standardizing human brain parcellations. *Scientific Data*, *8*(1), 78. https://doi.org/10.1038/s41597-021-00849-3

Martin, J. H., Radzyner, H. J., & Leonard, M. E. (2012). *Neuroanatomy text and atlas*. McGraw-Hill Medical.

Oswal, A., Beudel, M., Zrinzo, L., Limousin, P., Hariz, M., Foltynie, T., Litvak, V., & Brown, P. (2016). Deep brain stimulation modulates synchrony within spatially and spectrally distinct resting state networks in Parkinson’s disease. *Brain*, *139*(5), 1482–1496. https://doi.org/10.1093/brain/aww048

Quinn, A. J., Vidaurre, D., Abeysuriya, R., Becker, R., Nobre, A. C., & Woolrich, M. W. (2018). Task-Evoked Dynamic Network Analysis Through Hidden Markov Modeling. *Frontiers in Neuroscience*, *12*, 603. https://doi.org/10.3389/fnins.2018.00603

Sitnikova, T. A., Hughes, J. W., Ahlfors, S. P., Woolrich, M. W., & Salat, D. H. (2018). Short timescale abnormalities in the states of spontaneous synchrony in the functional neural networks in Alzheimer’s disease. *NeuroImage: Clinical*, *20*, 128–152. https://doi.org/10.1016/j.nicl.2018.05.028

Tait, L., Özkan, A., Szul, M. J., & Zhang, J. (2021). A systematic evaluation of source reconstruction of resting MEG of the human brain with a new high‐resolution atlas: Performance, precision, and parcellation. *Human Brain Mapping*, *42*(14), 4685–4707. https://doi.org/10.1002/hbm.25578

Van Essen, D. C., Smith, S. M., Barch, D. M., Behrens, T. E. J., Yacoub, E., & Ugurbil, K. (2013). The WU-Minn Human Connectome Project: An overview. *NeuroImage*, *80*, 62–79. https://doi.org/10.1016/j.neuroimage.2013.05.041

Vidaurre, D., Hunt, L. T., Quinn, A. J., Hunt, B. A. E., Brookes, M. J., Nobre, A. C., & Woolrich, M. W. (2018). Spontaneous cortical activity transiently organises into frequency specific phase-coupling networks. *Nature Communications*, *9*(1), 2987. https://doi.org/10.1038/s41467-018-05316-z