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# Machine Learning Enabled Brain Segmentation for Small Animal Image Registration

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**Abstract** — Cross-subject and cross-study comparability of preclinical imaging data, whole-brain imaging data in particular, is contingent on the quality of registration to a standard reference space. Current methods for neuroimaging rely on full image processing, with high varying intensities outside the brain Region Of Interest that interfere with registration. Applying the processing to a masked image improves the quality of the latter. Here, we present as an additional step in a small animal brain imaging registration workflow, a deep learning enabled framework for segmentation of brain tissue in functional and structural MR images.

## Background

To make meaningful comparisons across the subjects of a study, it is imperative that all scans lie in a standard reference frame. The common coordinate system enables a statistical evaluation of the likelihood of consistent activation across a group or, in other contexts, the differences in anatomy between two groups. Because of variability both in animal anatomy and in animal preparation, the original MR acquired images are not defined in a common template space. To solve this issue, scans need to be remapped to a reference frame via registration [1, 2]. As reported by Ioanas et al. [3], the legacy approach for mouse-brain image registration is to modify the data in order to conform to pre-existing functions, designed and optimized for human brain imaging. This requires the mouse-data to be adapted to the processing function instead of vice-versa. [3] establishes a novel workflow, specifically designed for mouse brain imaging, and benchmarks it against the legacy procedure. While the reported performance increase is considerable, registration quality can be improved further by computing the transformation solely on the brain volume to reduce disturbances induced by intensity variations outside the brain region.

## The Improved Workflow

In-vivo as well as ex-vivo MRI head scans, present higher variability in the viscerocranial and extracra-

nial tissue than in the neurocranium and the brain region of interest. Usage of unmasked (i.e. non brain extracted) data can thus lead to stretching or skewing of the brain during the registration process.

We lay out a preparatory step to improve brain registration by specifically extracting the brain volume from the MRI scans. Our solution utilises a machine learning enabled brain tissue classifier, and the software implementation is formulated to integrate with the SAMRI Generic workflow [3], in order to ensure broader usability and reproducible benchmarking. It creates a mask of the brain region using a classifier, which is then used to extract the region of interest. Two classifiers were trained, one for scans acquired with RARE sequences yielding  $T_2$ -weighted contrast and one scans acquired with gradient-echo EPI sequences yielding either BOLD [4] and CBV [5] contrasts. The brain extraction nodes of the workflow return both the masked input and the binary mask. The latter is used to constrain image similarity metric estimation on the relevant region of interest, while the extracted brain volume is used to compute the registration transformation.

## The Classifier

The assignment of “brain” and “not brain” annotation to each voxel in the scans is performed by a deep learning method. In recent years it has been shown that convolutional neural network give the best results for semantic image segmentation in terms of precision and flexibility [6, 7]. Training a neural network into a classifier is a supervised method. This means that the model needs to learn its parameters based on observations of data.

To improve general-purpose application, training examples need to be drawn from a usually unknown probability distribution, which is expected to be representative of the space of occurrences. We set up an occurrence space from which the data of interest is drawn, consisting of all the different mouse brain MRI data sets coming from multiple experiments, with their corresponding labels. Based on an approximation of the occurrence space, the network builds a general model that enables it to extrapolate and produce sufficiently accurate predictions in new cases.

Manually creating annotations as required to train a deep-learning classifier for high-resolution data is often infeasible, since it requires manual expert segmentation of vast amounts of slices.

As a training dataset, we use scans which were pre-processed with the SAMRI Generic workflow. This data thus contains scans mapped onto a bregma-centered standard [3] space derived from the Toronto Hospital for Sick Children Mouse Imaging Center brain template [8]. A template-based mask is available in the same reference space, and constitutes a ground truth estimation. As registration in the absence of brain extraction is prone to imperfections, the mask does not always align perfectly with the brain region of every slice.

While our purpose was to create a workflow that generates better masks than the one from the template space, we show that the latter can be used as training data for the deep-learning model, by applying small changes to it.

## Evaluation

For the quality control of the workflow, we first evaluate the classification process, followed by a benchmark between the Generic and the improved (Generic Masked) workflow.

### Segmentation

Quality control of our classifier is difficult in the sense that it should predict a better mask than the template. Nevertheless, it is useful to verify whether the output is similar, as it should be. As a similarity metric we have used the Dice score (see eq. (1)). The average Dice score taken on every slice of the test data set is  $D_{coef} = 0.952 \sim 1$ . The predictions thus have only minor changes in comparison with the template.

We evaluate the effects of our classifier on a full-fledged registration workflow via the benchmarking algorithms from [3]. We denote the original workflow as Generic and our modified version as Generic Masked.

### Workflow

We use an established palette of workflow evaluation metrics — inspecting volume and smoothness conservation, as well as downstream effects on basic functional analysis [3] — to benchmark the novel SAMRI Generic Masked workflow against the SAMRI Generic workflow. It is worth noting that the quality of the Generic workflow is already remarkable. Even slight improvements should be considered an amelioration.

### Volume Conservation

Volume Conservation Factor (VCF) [3] measures the registration induced deformation of the scanned brain, by computing the ratio of the brain volume before and after preprocessing. A positive ratio indicates that the

brain was stretched to fill the template space, while a negative ratio indicates that non-brain voxels were introduced in the template brain space. Volume conservation is highest for a VCF equal to 1, indicating that the preprocessing has no influence on the brain volume of the scans.

Evaluating a bootstrapped distribution of the respective Root Mean Squared Errors (RMSE) to 1, we report that the RMSE is sensitive to the workflow (RMSE of  $-0.02$ , 95%CI:  $-0.02$  to  $-0.02$ ) and the contrast-workflow interaction (RMSE of  $-0.02$ , 95%CI:  $-0.02$  to  $-0.02$ ).

A Wilcoxon signed-rank test on the absolute distance to 1 of both VCF distributions shows that the VCF is sensitive to the workflow (rank = 844.0, p = 0.044).

Moreover, the root mean squared error ratio favours the Generic Masked workflow ( $\text{RMSE}_{G^*}/\text{RMSE}_G \simeq 0.61$ ).

Further, we note that there is a significant variance decrease in all conditions for the Generic Masked workflow (0.25-fold).

With respect to the data break-up by contrast (CBV versus BOLD, fig. 2a), we see no notable main effect for the contrast variable (VCF of  $-0.03$ , 95%CI:  $-0.06$  to  $-0.01$ ), nor do we report a notable effect for the contrast-workflow interaction (VCF of  $0.01$ , 95%CI:  $-0.02$  to  $0.04$ ).

### Smoothness Conservation

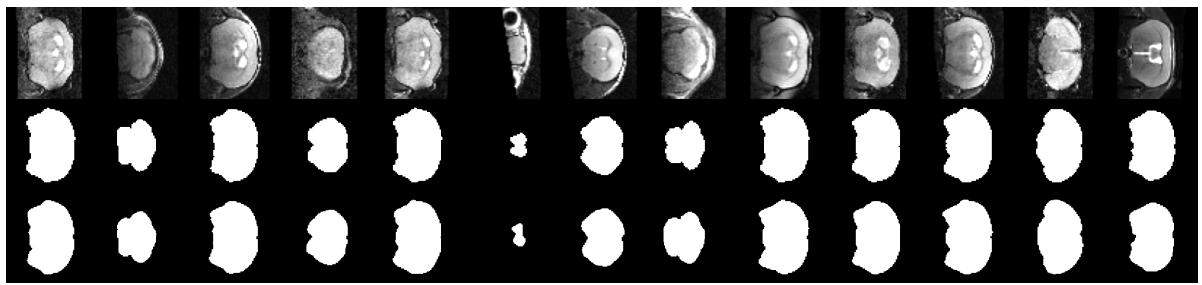
Smoothing is a popular tool employed by many pre-processing functions to increase the signal-to-noise ratio. Image smoothness comes at the cost of image contrast as well as feature saliency and has been shown to result in inferior anatomical alignment [9] due to the loss of spatial resolution. As an indicator of image smoothness induced by the workflow, the Smoothness Conservation Factor (SCF) [3] expresses the ratio between the smoothness of the preprocessed images and the smoothness of the original images. Smoothness Conservation is highest for a SCF equal to 1, indicating that the preprocessing does not influence image smoothness.

While the performance of the Generic SAMRI workflow is only slightly different from that of the Generic Masked workflow, the root mean squared error ratio favors the Generic Masked workflow ( $\text{RMSE}_{G^*}/\text{RMSE}_G \simeq 0.85$ ).

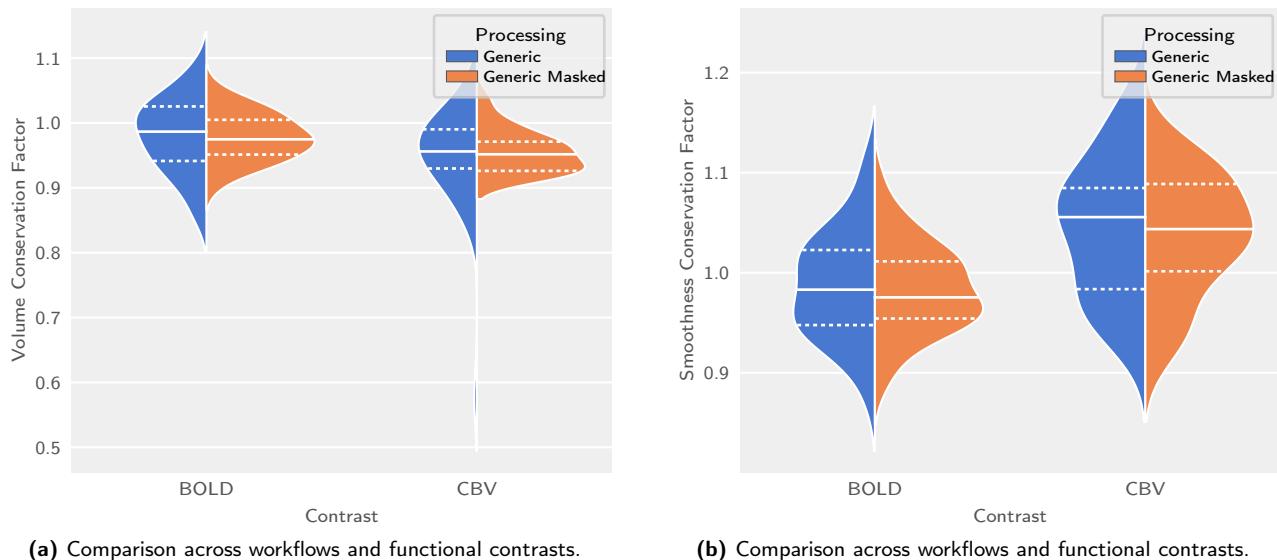
Descriptively, we observe that neither the Generic nor the Generic Masked workflow introduce a strong smoothing (SCF of  $0.00$ , 95%CI:  $-0.02$  to  $0.01$ ).

Further, we note that there is a notable variance decrease for the Generic Masked workflow (0.73-fold).

Given the break-up by contrast shown in fig. 2b, we see no effect for the contrast variable (SCF of  $0.06$ , 95%CI:  $0.03$  to  $0.08$ ) and the contrast-workflow interaction (SCF of  $0.00$ , 95%CI:  $-0.02$  to  $0.02$ ).



**Figure 1: The Classifier predicts a similar mask to the ground truth.** Randomly picked plots from the test set illustrate the predictions of the classifier. The first row presents the input image, the second the ground truth and the third row shows the predictions of the classifier.



**Figure 2: Both the SAMRI Generic and the Generic Masked workflow optimally and reliably conserve volume and smoothness, the latter showing values that are closely distributed to 1.** Plots of three target metrics, with coloured patch widths estimating distribution density, solid lines indicating the sample mean, and dashed lines indicate the inner quartiles.

## Functional Analysis

Functional Analysis expresses the significance detected across all voxels of a scan by computing the Mean Significance (MS) [3].

We observe that the Generic Masked level of the workflow variable does not introduce a notable significance loss (MS of  $-0.03$ , 95%CI:  $-0.05$  to  $0.00$ ). Furthermore, we note a slight variance decrease in all conditions for the Generic Masked workflow (0.94-fold).

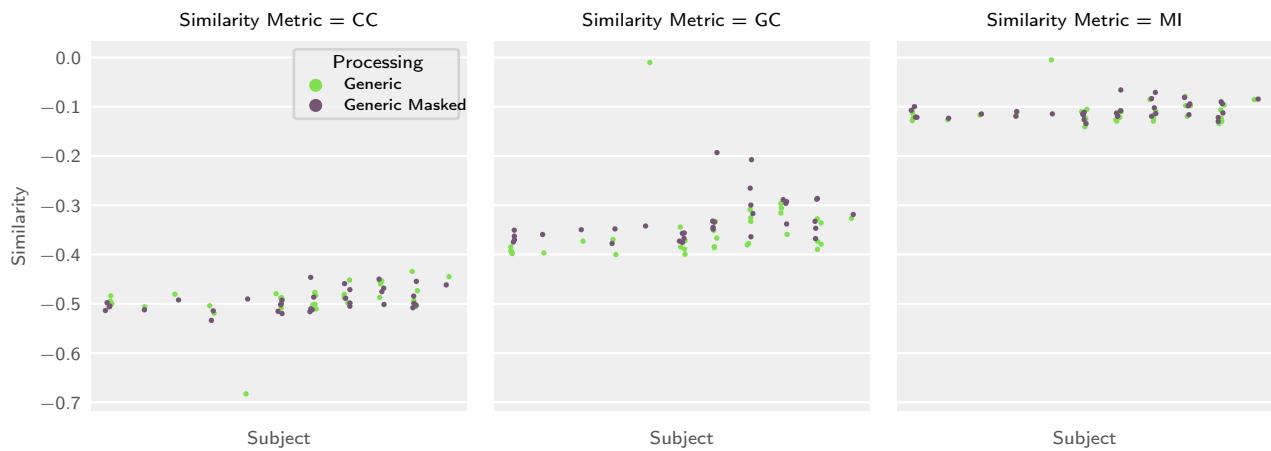
With respect to the data break-up by contrast (fig. S2), we see no notable main effect for the contrast variable (MS of  $-0.07$ , 95%CI:  $-0.85$  to  $0.71$ ).

## Variance Analysis

As an additional metric for the comparison between workflows, we evaluate if physiological meaningful variability is retained across repeated measurements.

It is based on the assumption that adult mouse brains retain size, shape, and implant position in the absence of intervention, throughout the 8 week study period [3]. Examining the similarity between the template and preprocessed scans, session-wise variability should be smaller than subject-wise variability. This comparison is performed using a type 3 ANOVA, modeling both the subject and the session variables. For this assessment three metrics are used, with maximal sensitivity to different features: Neighborhood Cross Correlation (CC, sensitive to localized correlation), Global Correlation (GC, sensitive to whole-image correlation), and Mutual Information (MI, sensitive to whole-image information similarity).

Figure 3 renders the similarity metric scores for both the SAMRI Generic and Generic Masked workflows. Both, the Generic and the Generic Masked workflow produce results which show a higher F-



**Figure 3: The Generic Masked workflow conserves subject-wise variability and minimizes trial-to-trial variability.** Swarmplots illustrate similarity metric scores of preprocessed images with respect to the corresponding workflow template, plotted across subjects (separated into x-axis bins) and sessions (individual points in each x-axis bin), for the CBV contrast.

statistic for the subject than for the session variable. For the Generic Masked workflow, F-statistics show: CC (subject:  $F_{10,19} = 7.498, p = 9.63 \times 10^{-5}$ , session:  $F_{4,19} = 3.808, p = 0.019$ ), GC (subject:  $F_{10,19} = 4.994, p = 0.0013$ , session:  $F_{4,19} = 1.586, p = 0.22$ ), and MI (subject:  $F_{10,19} = 1.266, p = 0.31$ , session:  $F_{4,19} = 3.14, p = 0.039$ ).

For the Generic SAMRI workflow, resulting data F-statistics show: CC (subject:  $F_{10,19} = 6.702, p = 0.00021$ , session:  $F_{4,19} = 2.753, p = 0.058$ ), GC (subject:  $F_{10,19} = 2.316, p = 0.055$ , session:  $F_{4,19} = 1.889, p = 0.15$ ), and MI (subject:  $F_{10,19} = 2.529, p = 0.039$ , session:  $F_{4,19} = 1.67, p = 0.2$ ).

## Discussion

The classifier improves the volume conservation, smoothness conservation, and session-to-session consistency of the SAMRI Generic workflow in terms of precision while conserving accuracy.

Region assignment validity is also revealed in a qualitative examination of higher-level functional maps (fig. S3), where both the Generic and the Generic Masked workflow provide accurate coverage of the sampled volume for both BOLD and CBV fMRI data.

These benefits of the classifier are robust to the functional contrast (figs. 2a and 2b), with the Generic Masking workflow being less or equally susceptible to the contrast variable, when compared to the Generic workflow.

The classifier improves the performance of the SAMRI Generic workflow, making these accessible in the same interface with the same advantages in terms of transparency, parametrization, ease of package management, and non-destructive metadata management. The complete workflow of this report is fully

reproducible and thus easily verifiable. We make public the functions used for the masking in the workflow as well as those used to train the classifier, through the *mlebe* [10] python package.

Our workflow has the advantage that the performance of a Neural Network can increase when trained further with new data. The FOSS distribution model for both the classifier and workflow, as well as the article, allows users to easily take advantage of the classifier extendability and recreate the steps described herein. Registering new data with the Generic Maksed workflow can increase the size of the training data set of the classifier. After removing possibly bad registrations, the latter can be trained again, which will improve its generalisation capability. Another advantage of the trainability of the classifier and the openly published code is that this workflow can be adapted to a wast variety of data types.

## Conclusion

We present a remodeled version of the SAMRI Genetic registration workflow, which offers several advantages summarized by established metrics for data features commonly biased by registration. Comparison with the original SAMRI Generic workflow revealed superior performance of the SAMRI Generic Masked workflow in terms of volume and smoothness conservation, as well as variance structure across subjects and sessions. The easily accessible, optimized registration parameters of the SAMRI Generic Workflow as well as the open source code to the classifier training functions make the pipeline transferable to any other imaging applications. The open source software choices in both the workflow and this article's source code empower users to better verify, understand, remix, and reuse our work.

## Methods

For the benchmarking of the two workflows, the same methods that are described in the original paper have been applied in this work. A more detailed description can be found there.

### Model

As the architecture of the classifier, the U-Net from Ronneberger et al [7] was chosen based on its high performance in the field of biomedical image segmentation. This is a convolutional neural network that consists of a contracting path that captures context in addition to a symmetric expanding path that enables precise localization. Localization in this context means that a class label is assigned to each pixel. We used the U-Net implementation from zhixuhao [11], written in Keras. Keras is a high-level neural networks API, written in Python and capable of running on top of TensorFlow, CNTK, or Theano. It allows for easily readable code and thus makes the workflow easier to reproduce.

The implementation of the U-Net from zhixuhao has, in addition to the original architecture, two drop-out layers. A drop-out layer randomly sets a fraction of input units from the layer to 0 at each update during training time. The set fraction rate is 0.5. It is known that dropout helps prevent overfitting and greatly improves the performance of deep learning models [12].

The model was trained using the Dice loss, which is computed from the Dice score. It calculates the similarity of two binary samples X and Y with

$$D_{coef} = \frac{2|X \cap Y|}{|X| + |Y|} \quad (1)$$

It is a quantity ranging from 0 to 1 that is to be maximized. The loss is then calculated with  $1 - D_{coef}$ . Because the Dice loss is not differentiable, small changes need to be made. In our case, the two samples to be compared are normalized, grey valued images and are thus not binary but have values between 0 and 1. Additionally, instead of using the logical operation *and*, element wise products are used to approximate the non-differentiable intersection operation. To avoid a division by zero, +1 is added on the numerator and denominator.

Because many more pixels in the masks are 0 than 1, there is a class imbalance problem. This is a problem because in this case a false positive gives a much higher loss than a false negative. For example, predicting only black would give an acceptable loss, while predicting only white pixels would not. Using the Dice coefficient as a loss function for training should make it invariant to this class imbalance problem as stated by Fausto Milletari et al. in [13].

### Data Set

The data set consists of 3D MR images taken from an aggregation of three studies: irsabi [14], opfvta [15], drlfom [16] and other unpublished data, acquired with similar parameters.

The measured animals were fitted with an optic fiber implant ( $l = 3.2\text{ mm}$   $d = 400\text{ }\mu\text{m}$ ) targeting the Dorsal Raphe (DR) nucleus in the brain stem. Using this dataset shows that the classifier is robust to these types of experiment setups.

Images from the irsabi study are only used for quality control of the registration and are thus unknown to the classifier. It is the same dataset that was used to benchmark the Generic workflow in the original paper and thus allows for a better estimation of the general performance of our improved pipeline.

The images are transformed into a standard space using a template mask via SAMRI [17] and are thus defined in the same affine space. SAMRI is a data analysis package of the ETH/UZH Institute for Biomedical Engineering. It is equipped with an optimized registration workflow and standard geometric space for small animal brain imaging [3].

Because of variance in mouse brain anatomy and in the experiment setup, some of the transformed data do not overlap perfectly with the reference template. To filter these images out, most of the incongruent slices were removed manually from the data set.

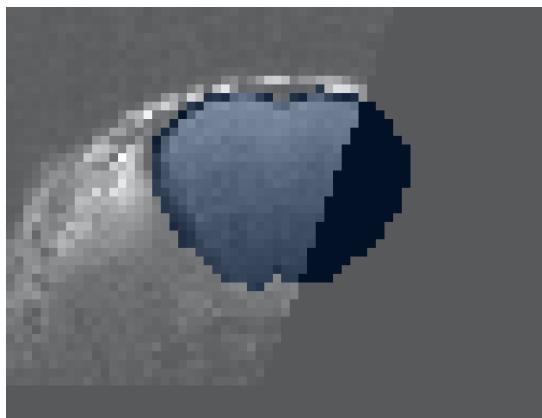
For the registration of the images, a padding was needed to make the originally not affine space affine. As a result, the 3D volumes present many zero-valued slices, some of them overlapping with the mask.

Since it is not wanted for the model to predict a mask on black slices, the mask is set to zero where the image is zero-valued. Because some pixels representing the brain tissue are zero-valued, holes result from this operation. To patch these, the function *binary\_fill\_holes* from *scipy.ndimage.morphology* [18] is used. An example of the preprocessing can be seen in fig. 4.

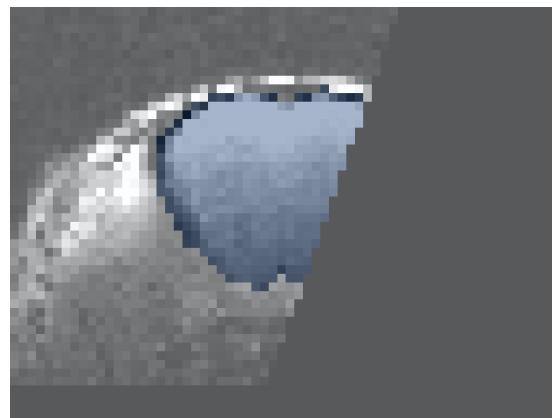
In the coronal view, each slice of the transformed data is originally of shape (63, 48), matching the reference space resolution of  $200\text{ }\mu\text{m}$ . It is then reshaped into (128, 128) by first zero-padding the smaller dimension to the same size as the bigger one and then reshaping the image into 128 using the function *cv2.resize* from the *opencv* python package [19].

Finally, the images are normalized by first clipping them from the minimum to the 99th percentile of the data to remove outliers and then divided by the maximum.

The data set is separated into Training, Validation and Test sets such that 90% of the total data are used for training and validation while 10% are used for testing. This is done with the help of the function *train\_test\_split* from the package *sklearn.model\_selection* [20]. The Validation set is used for the optimization of hyperparameters while



(a) Example of an unpreprocessed slice.



(b) Example of a preprocessed slice.

**Figure 4: The preprocessing removes the mask there, where the image-pixelvalues are 0.** Plots of the same image, superposed with the template mask, with and without preprocessing.

the Test set is used as a measure of extrapolation capability.

### Data Augmentation

Because of diverse settings in the experiment setup, including animal manipulations causing artifacts, MR image quality can differ substantially between labs and even individual study populations. To account for these variations, we apply an extensive set of transformations to our data. This includes rotations of up to  $90^\circ$ , a width and height shift range of 30 pixels, a shear range of 0.5 pixels, zoom range of 0.3, brightness range of (0.7, 1.3) and horizontal as well as vertical flips. Additionally a gaussian noise with a variance range of (0, 0.001) is added to the image.

This not only increases the data set size but also makes it more representative of the general data distribution of mice brain MR images and results in a model with a better generalization capability.

Many more sophisticated methods have been tested, but it has been shown that one of the more successful data augmentation strategies is the simple transformations mentioned above [21].

### Training

The model was trained slice wise, with the coronal view and 600 as the maximum number of epochs. The coronal view was chosen over the axial one, because the shapes of the masks are much simpler in the coronal view and thus easier to learn for the network.

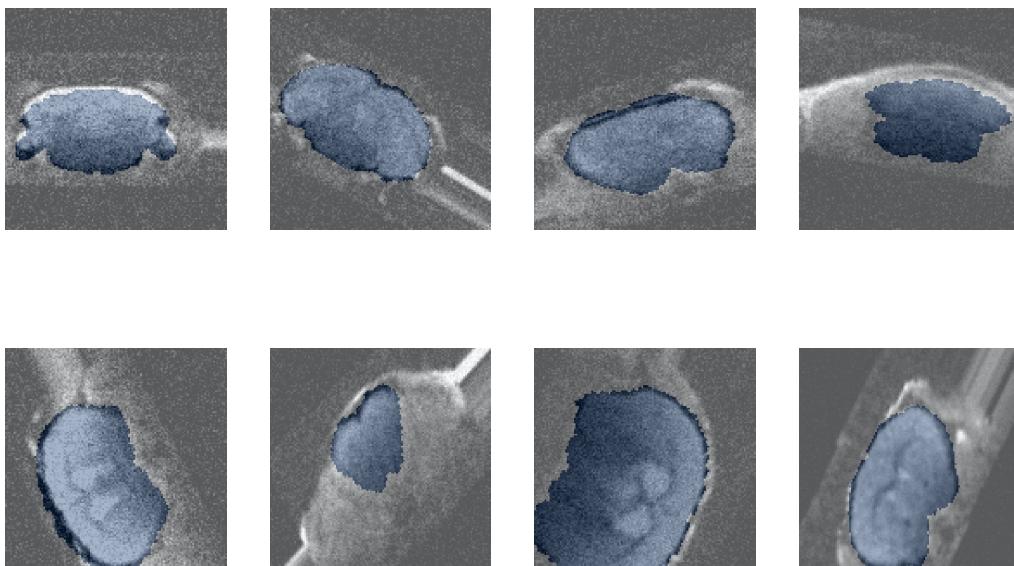
Additionally, the coronal view has the advantage of higher resolution as the MR images were recorded coronally.

To improve the learning process of the network, two callbacks from Keras were used [22]. "*ReduceLROnPlateau*" reduces the learning rate

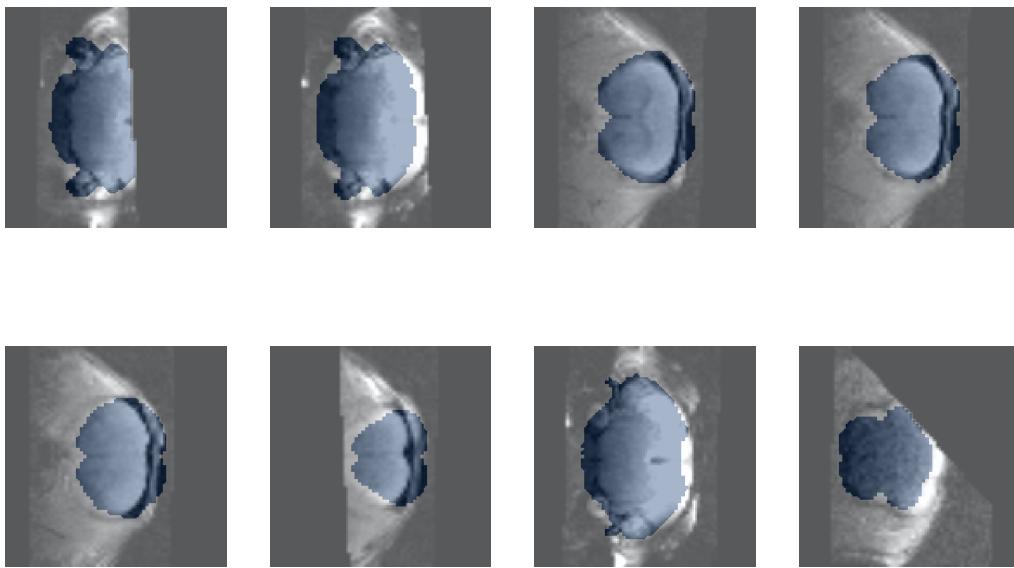
when the validation loss has stopped improving and "*EarlyStopping*" stops the training when the validation loss has stopped improving for a number of epochs. The latter reduces computation time and prevents overfitting.

### Masking

To improve the SAMRI registration workflow, an additional node is implemented where the images are masked, such that only the brain region remains. To alleviate the task of the classifier, the image is first bias-corrected using the "*N4BiasFieldCorrection*" function of the ANTs package, with spatial parameters used in the samri functions. The image is then resampled into the resolution of the template space, which has a voxel size of  $0.2 \times 0.2 \times 0.2$ . This is done with the *Resample* command from the FSL library which is an analysis tool for FMRI, MRI and DTI brain imaging data [23]. Then, the image is preprocessed using the operations described in section 5.2. Since the classifier was trained to predict on images of shape (128, 128), the input needs to be reshaped. The slice-wise predictions of the model are reconstructed to a 3D mask via the command *Nift1Image* from the neuroimaging python package nibabel [24]. This is done using the same affine space as the input image. The latter is then reshaped into the original shape inverting the preprocessing step, either with the opencv resize method or by cropping. Additionally, the binary mask is resampled into its original affine space, before being multiplied with the brain image to extract the ROI. The workflow then continues with only the Region Of Interest as the image.



**Figure 5:** Augmented samples from the Training set.



**Figure 6:** Slices where the mask includes too much outer-brain intensities are excluded from the data set. Examples from the slices that were excluded from the data set. The mask is shown in blue, on top of the brain image.

## Metrics

The VCF uses the 66<sup>th</sup> voxel intensity percentile of the raw scan before any processing as definition of the brain volume. The VCF is then obtained with eq. (2), where  $v$  is the voxel volume in the original space,  $v'$  the voxel volume in the transformed space,  $n$  the number of voxels in the original space,  $m$  the number of voxels in the transformed space,  $s$  a voxel value sampled from the vector  $S$  containing all values in the original data, and  $s'$  a voxel value sampled from the transformed data.

$$VCF = \frac{v' \sum_{i=1}^m [s'_i \geq P_{66}(S)]}{v \sum_{i=1}^n [s_i \geq P_{66}(S)]} = \frac{v' \sum_{i=1}^m [s'_i \geq P_{66}(S)]}{v \lceil 0.66n \rceil} \quad (2)$$

The bootstrapped distribution of the RMSE (eq. (3)) is obtained by resampling the VCF distributions 10000 times with replacement, and computing the RMSE for every sample.

$$RMSE = \sqrt{\text{mean}((1 - VCF)^2)} \quad (3)$$

The SCF metric is based on the ratio of smoothness before and after processing. It is obtained via eq. (4), where  $r$  is the distance of two amplitude distribution samples,  $a$  is the relative weight of the Gaussian term in the model,  $b$  is the width of the Gaussian and  $c$  the decay of the mono-exponential term [25].

$$ACF(r) = a * e^{-r^2/(2*b^2)} + (1 - a) + e^{-r/c} \quad (4)$$

The for the MS relevant statistical power is obtained via the negative logarithm of first-level p-value maps. Voxelwise statistical estimates for the probability that a time course could — by chance alone — be at least as well correlated with the stimulation regressor as the voxel time course measured are averaged via eq. (5), where  $n$  represents the number of statistical estimates in the scan, and  $p$  is a p-value.

$$MS = \frac{\sum_{i=1}^n -\log(p_i)}{n} \quad (5)$$

## Data and Code Availability

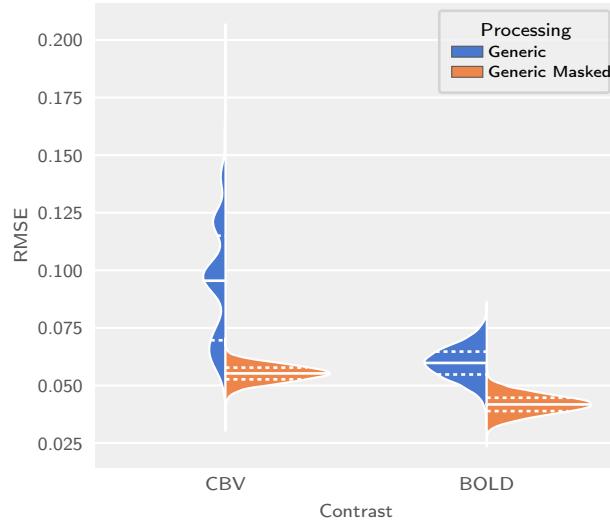
In addition to the workflow code [10, 26], we openly release the re-executable source code [27] for all statistics and figures in this document. The herein introduced novel method as well as the benchmarking are thus fully transparent and reusable for further data.

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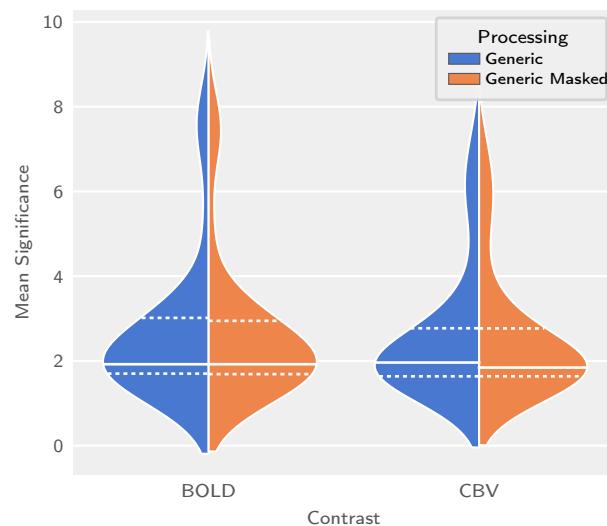
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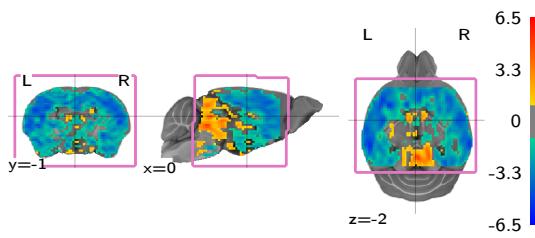
## Supplementary Materials



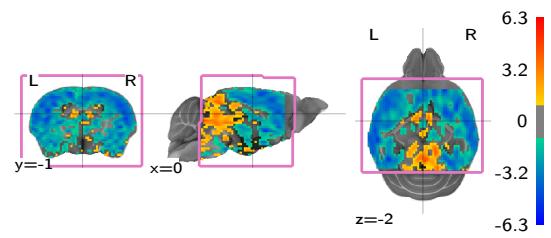
**Figure S1:** The Generic\* workflow shows much less variance than the Generic workflow. Comparison of a bootstrapped distribution of the root mean squared errors to 1, across workflows and functional contrasts.



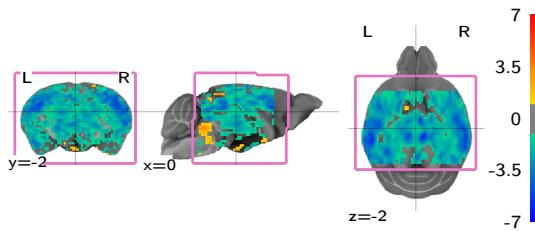
**Figure S2:** The Generic\* workflow does not introduce a significance loss. Comparison across workflows and functional contrasts.



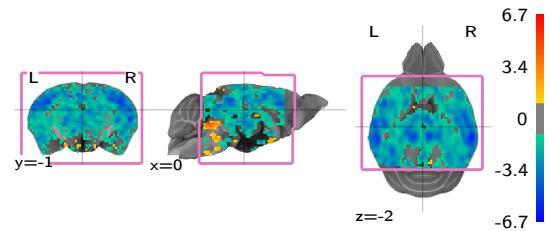
**(a)** Generic workflow with CBV map, showing correct slice orientation and coverage correctly bounded to the acquisition area.



**(b)** Generic\* workflow with CBV map, showing correct slice orientation and coverage correctly bounded to the acquisition area.

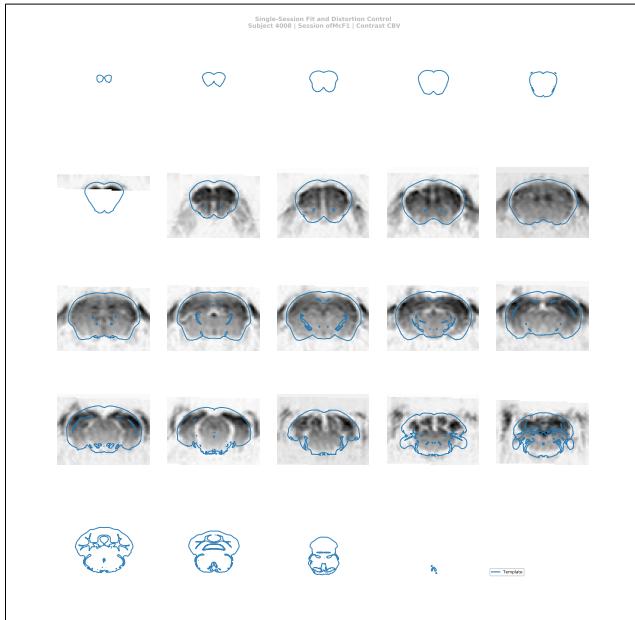


**(c)** Generic workflow with BOLD map, showing correct slice orientation and coverage correctly bounded to the acquisition area.

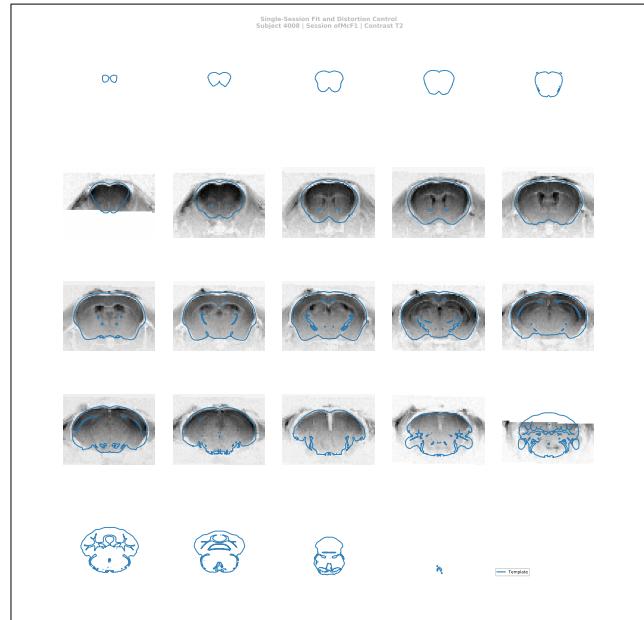


**(d)** Generic\* workflow with BOLD map, showing correct slice orientation and coverage correctly bounded to the acquisition area.

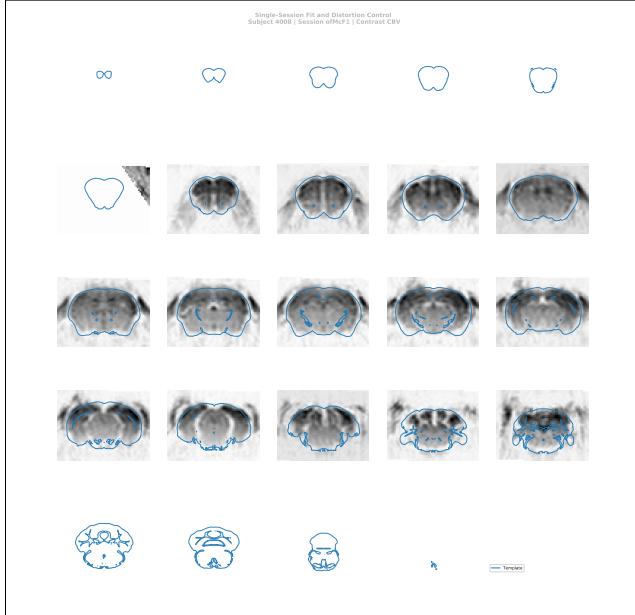
**Figure S3: The Generic\* workflow does not induce statistic coverage misalignment nor does it induce overflow of the statistic maps into adjacent anatomical regions.** Illustrated are multiplanar depictions of second-level omnibus statistic maps separately evaluating CBV and BOLD scans, and thresholded at  $|t| \geq 2$ . The acquisition area is bracketed in pink, and in comparing it to statistic coverage it is important to note that the latter is always underestimated, as the omnibus statistic contrast is only defined for voxels captured in every evaluated scan.



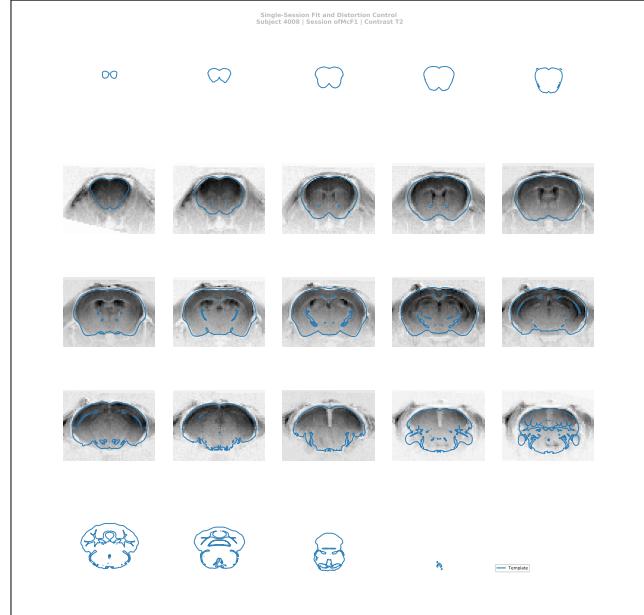
**(a)** SAMRI Generic workflow, note the undistorted mapping and conservative smoothing.



**(b)** SAMRI Generic workflow, inspecting the structural scan intermediary; note the undistorted mapping and conservative smoothing.

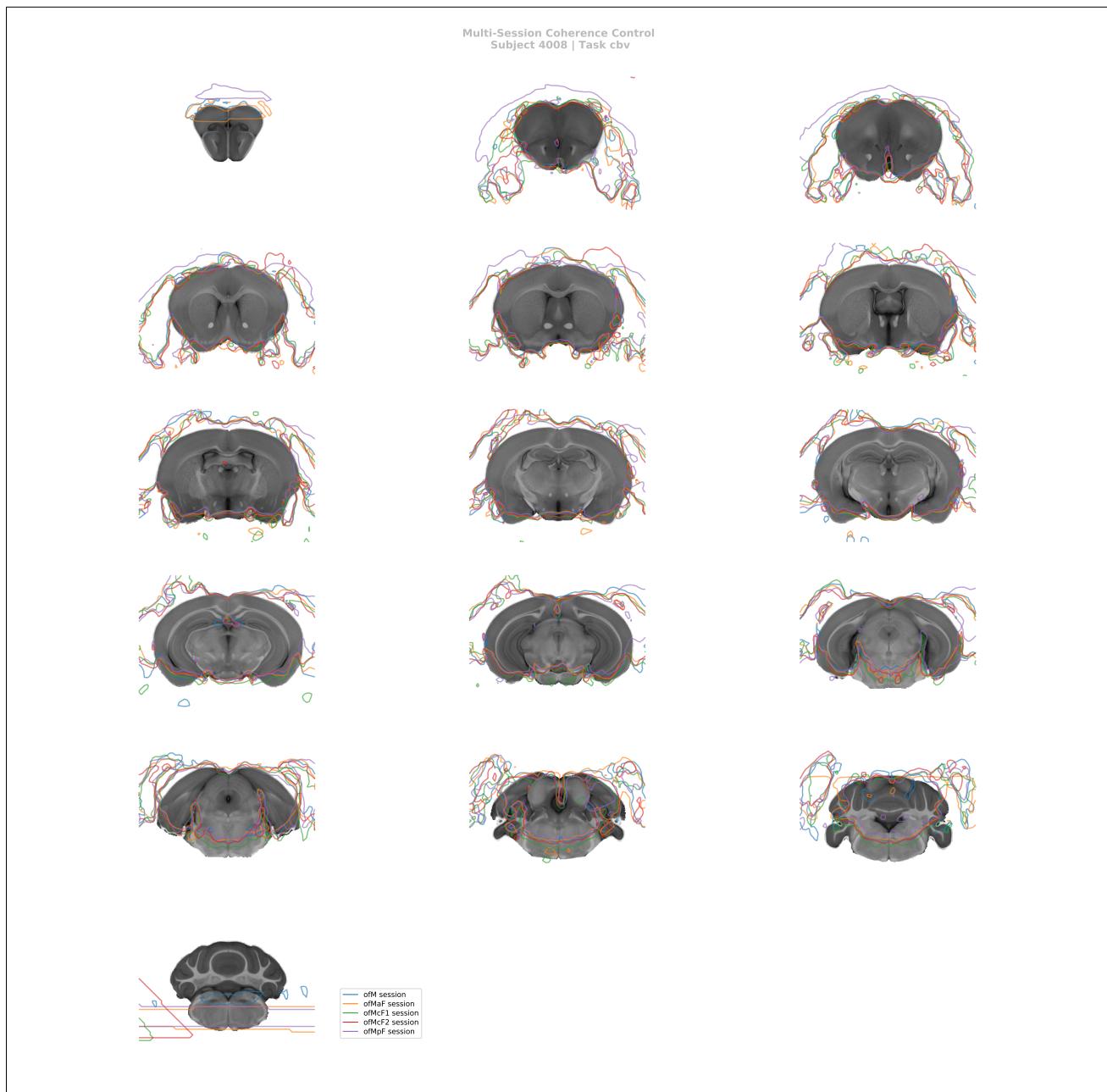


**(c)** SAMRI Generic Masked workflow, note the undistorted mapping and conservative smoothing.

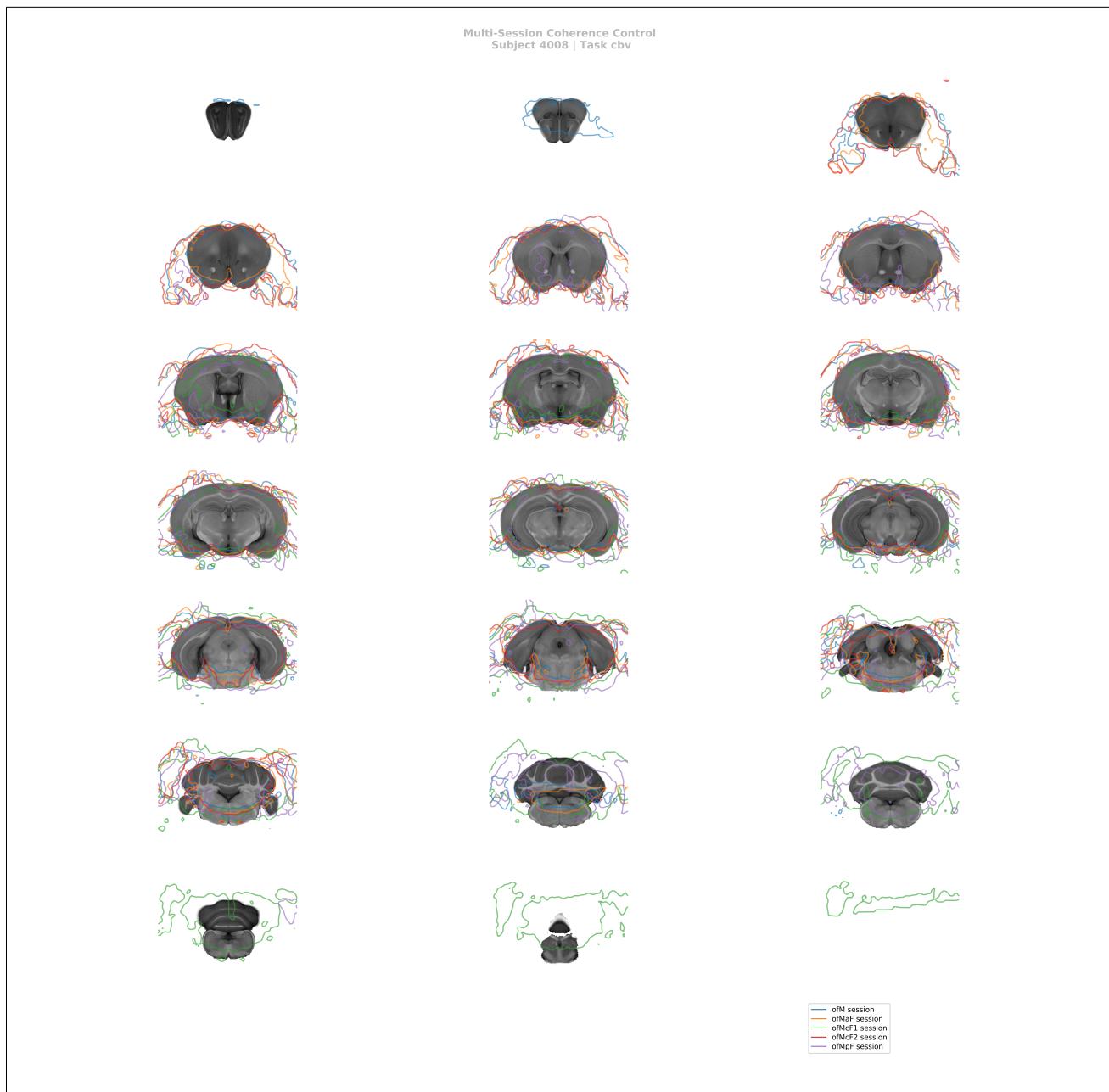


**(d)** SAMRI Generic Masked workflow, inspecting the structural scan intermediary; note the undistorted mapping and conservative smoothing.

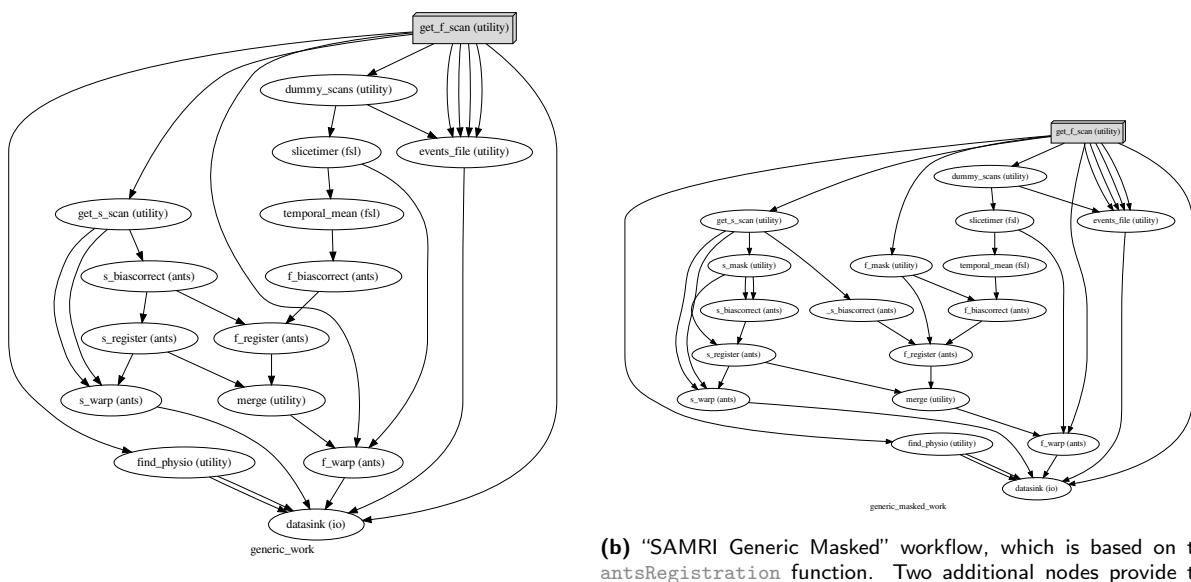
**Figure S4: The SAMRI Generic\* provides a more accurate coverage of the template space.** Depicted are automatically created operator overview graphics, which allow a slice-by-slice (spacing analogous to acquisition) inspection of the registration fit. This representation affords a particularly detailed view of the preprocessed MRI data, and highly accurate template contours.



**Figure S5: The SAMRI Generic workflow consistently maps high-salience features such as the implant site across sessions.** Automatically created operator overview graphic, allowing a slice-by-slice (spacing analogous to acquisition) inspection of registration coherence. This representation permits a coarse assessment of registration consistency for multiple sessions — though at the cost of some clarity. Particularly, this visualization, allows an operator to track the position of high-amplitude fixed features across scans in order to ascertain coherence (similarly to what is automatically assessed by the Variance analysis of the session factor).



**Figure S6: The SAMRI Generic Masked workflow consistently maps high-salience features such as the implant site across sessions.** Automatically created operator overview graphic, allowing a slice-by-slice (spacing analogous to acquisition) inspection of registration coherence. This representation permits a coarse assessment of registration consistency for multiple sessions — though at the cost of some clarity. Particularly, this visualization, allows an operator to track the position of high-amplitude fixed features across scans in order to ascertain coherence (similarly to what is automatically assessed by the Variance analysis of the session factor).



**Figure S7:** Directed acyclic graphs detailing the precise node names (as seen in the SAMRI source code) for the two alternate MRI registration workflows. The package correspondence of each processing node is appended in parentheses to the node name. The “utility” indication corresponds to nodes based on Python functions specific to the workflow, distributed alongside it, and dynamically wrapped via Nipype. The “extra\_interfaces” indication corresponds to nodes using explicitly defined Nipype-style interfaces, which are specific to the workflow and distributed alongside it.