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NeuroNorm: An R package to standardize multiple structural MRI

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ABSTRACT

Preprocessing of structural MRI involves multiple steps to clean and standardize data before further analysis. Typically, researchers use numerous tools to create tailored preprocessing workflows that adjust to their dataset. This process hinders research reproducibility and transparency. In this paper, we introduce `NeuroNorm`, a robust and reproducible preprocessing pipeline that addresses the challenges of preparing structural MRI data. `NeuroNorm` adapts its workflow to the input datasets without manual intervention and uses state-of-the-art methods to guarantee high-standard results. We demonstrate `NeuroNorm`'s strength by preprocessing hundreds of MRI scans from three different sources with specific parameters on image dimensions, voxel intensity ranges, patients characteristics, acquisition protocols and scanner type. The preprocessed images can be visually and analytically compared to each other as they share the same geometrical and intensity space. `NeuroNorm` supports clinicians and researchers with a robust, adaptive and comprehensible preprocessing pipeline, increasing and certifying the sensitivity and validity of subsequent analyses. `NeuroNorm` requires minimal user inputs and interaction, making it a user-friendly set of tools for users with basic programming experience.

1. Introduction

Magnetic resonance imaging (MRI) has transformed the human brain's study, especially brain disorders, since its inception in 1977. MRI is highly effective for identifying anatomical and structural changes in brain physiology by using brain tissue molecules' magnetic response [1]. Measures of abnormalities derived from structural MRI have been markedly practical regarding diagnosis and assessment of neurodegenerative diseases [2], mental disorders [3], and brain tumors [4]. Clinical trials have exploited MRI potential in the characterization of brain disorders and have established it as a reliable tool for both the diagnostic process and disease progression monitoring.

The analysis of structural MRI is a growing area of research. Over the last 20 years, the number of neuroimaging studies involving structural MRI have increased rapidly. From visual inspection to delimit brain regions [5,6] to automatic analytical methods to characterize disorders [7–9], structural MRI has become crucial in brain medical research. Furthermore, more and more research institutes, medical institutions and private companies are providing publicly available datasets. The importance of these datasets is evident in the neuroimaging research community, where studies using structural MRI from multiple sources, sites, scans, and subjects are more common in literature [10].

Although structural MRI is a powerful source of information, it is typically affected by different types of variability in the acquisition process [11]. For instance, head/body movements and anatomical dimensions are non-neuronal sources of variability derived from patient's particularities [12]. Additionally, other non-neuronal effects emerge from the characteristics of MRI scanners (e.g., protocols, sequences, and hardware calibration) [13]. The raw data require a set of corrections, known as preprocessing steps, to uncover the closest representation of the underlying brain structure. The preprocessing steps focus on identifying and minimizing the sources of noise and artifacts in the data before applying any subsequent processing and analysis [14]. Preprocessing ensures data cleaning and standardization to validate the interpretability and consistency of the analysis results.

Preprocessing workflows address two main aspects: the quality and the signal of the MRI scans. The former reduces the noise to improve the signal, and the latter sets a specific geometric or intensity space to locate it. Standard preprocessing steps include inhomogeneity correction, spatial registration, spatial normalization, and intensity standardization. Furthermore, preprocessing may

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include further steps for denoising and transforming the signals, for instance, spatial smoothing for removing high frequencies on the signals [15] and image harmonization to eliminate scanner effects [16].

Tools for implementing most of the preprocessing steps are commonly available in native programming languages and distributed as software packages. Packages such as FreeSurfer [17], FSL [18], ANTs [19] and Insight Toolkit [20] are popular in the neuroimaging community, as they are open-source tools and freely accessible. However, given the extensive amount of tools, almost every neuroimaging study has its own preprocessing pipeline. This restrains the reproducibility of scientific results and limits the development of new studies [21]. In a realistic sense, the brain imaging research needs a robust, automatic and flexible preprocessing workflow that can adjust to numerous and diverse sources of MRI data and produce highly specified and coherent results.

This paper develops and validates a straightforward preprocessing workflow for structural MRI images to clean and standardize multiple MRI scans from multiple sites, patients, and studies. The `NeuroNorm` package proposes a preprocessing workflow that addresses both the denoising and transformation of the MRI signals while preparing the data for further analysis. We use state-of-the-art preprocessing methods to provide a comprehensive and robust pipeline to clean and normalize MRI sequences such as T_1-weighted, T_2-weighted, and FLAIR sequences. We illustrate our approach's power by preprocessing MRI scans of patients with neurodegenerative diseases from three different data sources (the Alzheimer's Disease Neuroimaging Initiative (ADNI), the Parkinson's Progression Markers Initiative (PPMI), and the Multiple Sclerosis database of the University Medical Center Ljubljana.). The resulting MRI images can be used for quantitative and qualitative in group-level and/or population-level studies.

2. The neuronorm workflow

2.1. Overview

`NeuroNorm` was developed to provide a robust and comfortable tool to prepare structural MRI scans for analysis.`NeuroNorm` is an easily accessible package that allows users to preprocess multiple MRI scans in an automated fashion using minimal user input. `NeuroNorm`, using state-of-the-art essential preprocessing steps, generates outputs that could be used in a broad spectrum of analysis such as voxel-based morphometry, volumetric measurements of regions of interest, deep learning algorithms, and more.

The `NeuroNorm` preprocessing pipeline is implemented in R, using the integrated development environment (IDE) RStudio [22]. Its main functionalities translate as wrapper functions built from noted neuroimaging R packages such as `fslr`, `ANTs`, `extrantsr`, and `RAVEL` [23,19,24,25]. We propose an R package that selects each R package's best preprocessing algorithms and combines them to produce a fully automatic and advantageous implementation. We recommend installing the required packages to guarantee the correct performance of the `NeuroNorm` package.

The processing pipeline comprises a set of processes embedded within dynamic configurations depending on the input data, that is, the MRI sequences (T_1-weighted, T_2-weighted, and FLAIR). The pipeline is made of five sequential steps to correct and standardize the raw MRI images: imhomogeneity correction, spatial registration (within subject and to template), skull stripping, brain segmentation and intensity normalization (Fig. 1). `NeuroNorm` uses the data structure to identify the available MRI sequences and adjusts the preprocessing pipeline accordingly. Furthermore, `NeuroNorm` adapts to missing sequences and multiple scans from different patients and sites.

Inhomogeneity correction, also known as bias field correction, is a technique to adjust low-frequency undesirable signals that corrupts MRI images because of the inhomogeneities in the MRI scanners' magnetic fields. A bias field blurs images, thus reducing their contents and changing the intensity voxel values, so the same tissue has different grey level distribution across the image [26]. Inhomogeneity correction regulates the intensity values voxel-wise based on a particular tissue and allows further analysis such as segmentation and classification, which assume spatial invariance of the MRI scans. In the `Neuronorm` package, the improved N3 Bias Correction named N4 [27] is implemented.

Spatial registration refers to the process of aligning two images so that their standard anatomical features overlap and their differences are emphasized and readily visible [28]. Spatial registration performs spatial transformations to multiple images to make locations of voxels have a similar interpretation across the cerebral anatomical structures. Specific voxels in particular locations can be only constrained in brains with equivalent spatial domains.

During an MRI session, a particular structural scan is obtained according to the subject's brain shape and layout and the scanner's particular parameters. Every image must have the same characteristics in resolution, size, and spatial distribution to conduct a group or a population-level analysis. This type of registration is called registration to a template.

Since the aim of `Neuronorm` is to make comparable MRI images from different sources and patients, a non-linear symmetric diffeomorphic image registration [29] method was used to transform the scans into a reference template. However, before registering to a template, the T_2-weighted and FLAIR sequences must be translated (co-registered) to the T_1-weighted because population templates are mainly designed for the T_1-weighted sequence. For each subject, we implemented a rigid linear transformation that allows a fast and straightforward registration due to the shared dimensions of the subject's brain and skull. The literature suggests the brain atlas of the Montreal Neurological Institute (MNI) due to its high-spatial-resolution and unbiased properties for registration to a template. The MNI template is a standard MRI template for average population [28]. This template defines a representative brain of the population derived from averaging the dimensions, size, and brain MRI locations from 152 healthy individuals.

Skull Stripping removes non-brain tissue such as the skull and neck from an MRI scan of the whole head. Since most projects focus on the brain tissue, non-brain voxel areas are deleted from the MRI data. The brain extraction is performed by masking the registered sequences using the brain mask of the population template.

Brain segmentation involves assigning to the voxels of an MRI scan a class label value representing the white matter, grey matter, and cerebrospinal fluid tissues. In `Neuronorm`, the brain segmentation via Hidden Markov Random Field (HMRF) [30] is used. This algorithm is widely adopted in image segmentation due to its classification nature and its spatial context properties. In brain imaging, HMRF models segment the brain in selected classes, usually cerebral structures, whilst also correcting spatial intensity variations. It is a robust and reliable method insensible to noise with probabilistic volume tissue segmentation.

Intensity normalization ensures comparability across images by bringing the intensities to a standard scale across patients [28]. MRI intensities are acquired in arbitrary units, making them incomparable across sites and between subjects. Even MRI scans acquired with the same protocol can not be compared. This phenomenon affects the performance, prediction, and inference of further MRI analysis. Intensity normalization is a crucial step before performing between-subject or between-time intensity comparisons at the voxel level.

`Neuronorm` uses the Removal of Artificial Voxel Effect by Linear regression (RAVEL) algorithm [25] to normalize the voxel intensi-

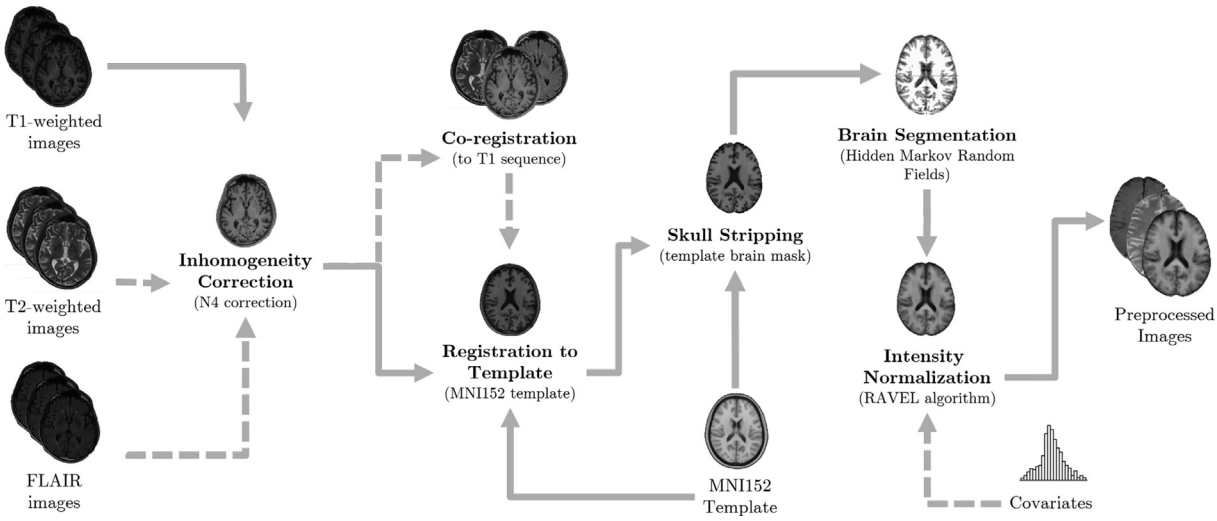


Fig. 1. Preprocessing pipeline implemented in the `NeuroNorm` package. It adapts the pipeline configuration based on the input MRI sequences. *NeuroNorm* supports multiple MRI scans from the three compatible modalities. T_2-weighted and FLAIR images are optional for the co-registration step, as well as the covariates for the intensity normalization process.

ties. The method removes present unwanted variation after a white stripe intensity normalization, a robust method based on parameters obtained from a sample of normal-appearing white matter. The RAVEL algorithm normalizes the voxel intensity values by decomposing the intensities' variation into a biological component (clinical covariates) and technical variation (scan effects). RAVEL algorithm uses covariates to produce the normalized voxel intensities for each MRI. If no covariates are provided, the RAVEL algorithm becomes a White Stripe technique[31]. The White Stripe normalization method normalizes the intensity of the voxels accounting for the natural balance of the brain tissues. White stripe ensures preserving brain abnormalities or damaged tissue that would be obscured with traditional normalization methods.

2.2. Comparison to alternative preprocessing tools

`Neuronorm`, as an R package, offers distinct advantages over its counterparts due to its fully automated pipeline, eliminating the need for users to manually apply each preprocessing step sequentially. By integrating a comprehensive set of preprocessing algorithms into a unified and automated process, `Neuronorm` streamlines the preprocessing workflow and reduces the burden on researchers and clinicians. Instead of navigating through complex manual procedures such as those in FreeSurfer, FSL and Insight Toolkit, users can simply provide the input data and customize the algorithms according to their specific preprocessing requirements. It as well alleviates time-consuming and error-prone challenges associated to the manual execution of preprocessing steps. Another advantage of `Neuronorm` compared to existing preprocessing tool software, is that it guarantees reproducibility and reduces the data variability by automating the application of preprocessing algorithms. In contrast, existing preprocessing software tools such as FreeSurfer and FSL, although offering semi-automatic pipelines, either require extensive batch scripting knowledge to handle large numbers of MRIs or rely on outdated preprocessing algorithms. Furthermore, `Neuronorm`'s automation facilitates scalability, enabling efficient processing of large datasets. With the ever-increasing availability of neuroimaging data from multicenter studies and open-access repositories, the ability to preprocess a considerable number of images rapidly becomes paramount. `Neuronorm`'s automated pipeline empowers researchers to tackle this demanding task effectively, saving time and effort while ensuring the quality and consistency of preprocessing across diverse datasets.

The field of neuroimaging research heavily relies on accurate preprocessing of MRI data to ensure reliable and meaningful results of brain imaging analysis. In this context, the selection of appropriate software tools plays a crucial role. `Neuronorm`, specifically designed for preprocessing multiple MRI datasets coming from different patients, sites and studies, offers a variety of state-of-the-art methods that differentiate it from other widely used brain imaging preprocessing software tools, including FreeSurfer, FSL, ANTs, and Insight Toolkit (Table 1). While `Neuronorm` shares and borrows preprocessing algorithms from well-known neuroimaging preprocessing tools, its success lies in integrating these algorithms into a fully automated pipeline, minimizing the need for human intervention.

`Neuronorm` provides both the N3 and improved N4 Bias correction algorithms for inhomogeneity correction, which none of the alternative tools, besides the ANTs software, offer comprehensively. Inhomogeneity correction plays a crucial role in eliminating intensity variations resulting from non-uniformities in MRI signals during data acquisition [26]. By incorporating both the N3 and N4 algorithms, `Neuronorm` allows researchers to choose the most appropriate correction method based on specific dataset characteristics, such as the level of noise present in the MRI signals.

Spatial registration, a critical step in the preprocessing of neuroimaging data, is also effectively supported by `Neuronorm`. Our software package offers both linear (Affine) and nonlinear (Symmetric Diffeomorphic Image Registration - SyN) transformation algorithms, providing users with the ability to achieve accurate normalization and anatomical alignment of brain images. While alternative tools also offer linear registration capabilities, the inclusion of a non-linear transformation algorithm within `Neuronorm` significantly enhances its capacity for advanced and precise spatial normalization. This feature proves particularly advantageous when investigating anatomical variations across subjects or time points, as it facilitates reliable inter-subject and longitudinal analyses [28].

`Neuronorm` includes as well brain extraction algorithms, aligning with the functionality of the alternative tools, to ensures that subsequent analysis focus solely on brain structures. One notable aspect of `Neuronorm` is its integration of the FMRIB's Automated Segmentation Tool (FAST) for brain segmentation. Our package

Table 1
Comparison of state-of-the-art preprocessing tasks for various brain imaging preprocessing tools and Neuronorm.

Task	Algorithm	Alternative preprocessing tools				Neuronorm
		FreeSurfer	FSL	ANTs	Insight Toolkit	
Imhomogeneity	N3	X	✓	✓	X	✓
Correction	N4	X	X	✓	✓	✓
Spatial	Affine	✓	✓	✓	✓	✓
Registration	SyN	✓	✓	✓	X	✓
Skull Stripping	Brain extraction	✓	✓	✓	✓	✓
Brain	FAST	X	✓	X	X	✓
Segmentation	Segmentation Tool	X	✓	X	X	✓
Intensity	RAVEL	X	X	X	X	✓
Normalization	White Strip	X	X	X	X	✓

borrows the FAST brain segmentation algorithm from the only package with its implementation, FSL. The FAST algorithm is an automatic robust and reliable segmentation method, compared to most finite mixture model-based methods such as Atropos Multivar-EM Segmentation and K-Means clustering available in ANTs and Insight Toolkit, respectively, as it is less sensitive to noise and skull border effects [30].

Intensity normalization algorithms play a pivotal role to analyse MRI data originating from different sites, scanners, patients and studies. In this regard, Neuronorm excels in being the only tool offering both the RAVEL and White Strip methods. The integration of these methods within Neuronorm's preprocessing pipeline enables researchers to address intensity variations stemming from various acquisition protocols or disease-related effects. By effectively normalizing intensities across images, Neuronorm ensures improved intra- and inter-imaging comparability while mitigating potential confounding factors that could compromise the accuracy of subsequent analyses. This capability proves essential in enhancing the reliability and validity of neuroimaging investigations dealing with multi-site or longitudinal MRI data.

3. Implementation and functionalities

3.1. Data structure

3.1.1. MRI scans

MRI scans must follow a specific data structure, so NeuroNorm will be able to identify their sequences correctly. We recommend a folder structure in which each patient represents a folder containing their corresponding MRI scans. Furthermore, the name of the MRI scan file must refer to the description of the sequence, that is, "T1", "T2" or "FLAIR". Fig. 2 shows an example of the required data structure. The MRI scan files must follow the NIfTI (Neuroimaging Informatics Technology Initiative) data format.

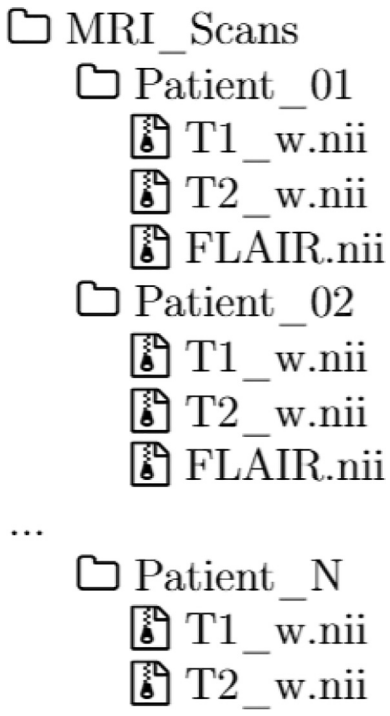


Fig. 2. Recommended folder structure.

3.1.2. Covariates

Most of the available MRI datasets will provide basic information about the scan patients, e.g., age, sex, disease type. RAVEL technique implemented in NeuroNorm uses this information as covariates to correct unwanted variation and normalize the voxel intensities. We suggest including covariates as long as these are available for all the MRI scans to preprocess for RAVEL to work correctly. Otherwise, the WhiteStripe technique will be utilized.

Table 2 displays an example of the covariates structure. The format can be an external CSV or a native R data frame. The number of rows of covariates must match the number of patients.

Table 2
Suggested structure of covariates. In this case, covariates are sex and age. More variables can be included if available.

Patient	Age	Sex
1	58	F
2	65	M
...	...	...
N	55	F

3.2. Data loading

The NeuroNorm preprocessing pipeline only requires two parameters. The first one refers to the folder containing the data (see data structure). The second parameter corresponds to the covariates of interest needed to perform the RAVEL intensity normalization.

We tested NeuroNorm with MRI data of 330 patients from different sources. However, the dissemination and use of such information is bounded by the sources own policies. We provide sample data of four patients including MRI images, covariates, and folder structure in a helper package called NeuroData for a reproducible example.

The sample data can be loaded with the following commands.

```
# Install and load package
install.packages("Neuronorm")
library(neuronorm)
# Get general folder
folder <- system.file("extdata", package =
  "neurodata")
# Get covariates
covariates <- system.file("covariates.txt",
  package = "neurodata")
# Read covariates information
clinical_info <- read.csv(file  = covariates, sep =
  ';')
```

3.3. Preprocessing

The function `preprocess_patients()` takes as input the folder containing the raw images and the covariates, applies the preprocessing pipeline to the input images, and creates preprocessed images for each process. First, the function checks for the MRI scan modalities and informs the user if any is missing. Since `NeuroNorm` adapts to the provided information, it is not necessary to have all the supported MRI sequences. However, the T_1-weighted sequence is mandatory.

```
# Preprocess MRI scans
paths_preprocess_patients <- preprocess_patients
  (folder, clinical_info)
```

The function also displays the folder currently in prepossessing and the steps involved. The messages will allow the user to track the function progress and assess its performance.

The RAVEL algorithm (intensity normalization) is applied after executing the other preprocessing steps in all patients. RAVEL requires every normalized, co-registered, skull stripped image as well as the covariates. If the latter is not provided, the White Stripe normalization method will be performed instead. This is the last step of the `NeuroNorm` preprocessing pipeline.

After executing the `preprocess_patients()` function, preprocessed images and a list of paths are created. The preprocessed images are located in the patient's folder. The list contains the images' relative paths for each preprocessing step to be loaded directly into R.

```
# Accesing the MRI preprocessed scan for patient
  one: RAVEL normalized.
paths_preprocess_patients$patient01$ravel
# Accesing the MRI preprocessed scan for patient
  two: skull stripped.
paths_preprocess_patients$patient02$stripped
```

To visualize the preprocessed images, the `orthographic()` function from the oro.nifti package can be used. For comparison purposes, we also include the visualization of the same MRI scan without preprocessing (Fig. 3b).

```
library('oro.nifti')
# visualize a fully preprocessed MRI scan for a
  patient.
preprocessed_img <- readNIfTI(file.path
  (paths_preprocess_patients$patient01$ravel))
orthographic(preprocessed_img)
# original MRI scan for the same patient
raw_img <- readNIfTI(file.path("/
  MRI_Scans/patient01/patient01_T1WKS.nii.gz"))
orthographic(raw_img)
```

Fig. 3 shows a raw MRI scan against a preprocessed one. In the processed MRI scan, the voxel intensities and locations were corrected. Also, subject-specific and scanner-specific effects were removed. The processed scan shares the spatial architecture and dimensions of the Montreal Neurological Institute (MNI) template brain atlas. This noise-free MRI scan can be used in further analysis, e.g., classification analysis.

Some `NeuroNorm` capabilities also work outside the `preprocess_patients()` function. For example, the function `preprocess_modalities()` preprocesses MRI scan sequences for just one patient. Furthermore, this function admits the user's preferred atlas template, inhomogeneity correction (N3 or N4 correction), and registering transformation (see supported transformations in the `antsRegistration()` function of the `ANTs` package). In this scenario, the intensity normalization algorithm is not applied since it requires multiple patients to be performed.

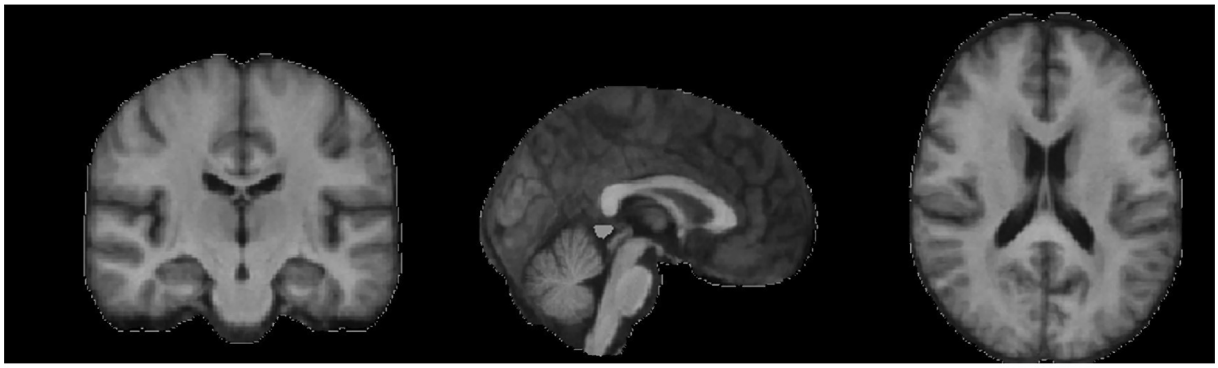
```
# Folder of the patient
patient_folder <- file.path(folder,"patient01")
## Getting the paths of the MRI scan sequences for
  one patient
## the NeuroNorm built-in function
  load_mri_patient() can be used for this.
sequences <- load_mri_patient(patient_folder)
## Getting preferred atlas template and template
  mask
## Using the MNI152 template available in the
  MNITemplate package
library(MNITemplate)
atlas <- getMNIPath()
atlas_mask <- readMNI("Brain_Mask")
## Preprocessing the patient's sequences
patient_preprocessed_mri <-
  preprocess_modalities(mri.patient = sequences,
folder.patient = patient_folder, modalities = c('
  T1','T2','FLAIR'), atlas = atlas, mask
  = atlas_mask, inhomogeneity = 'N4',
  transformation = 'SyN')
```

The RAVEL intensity normalization function can also be used alone. This is particularly useful for normalizing intensities of T_2-weighted and FLAIR sequences when only a few of them are provided.

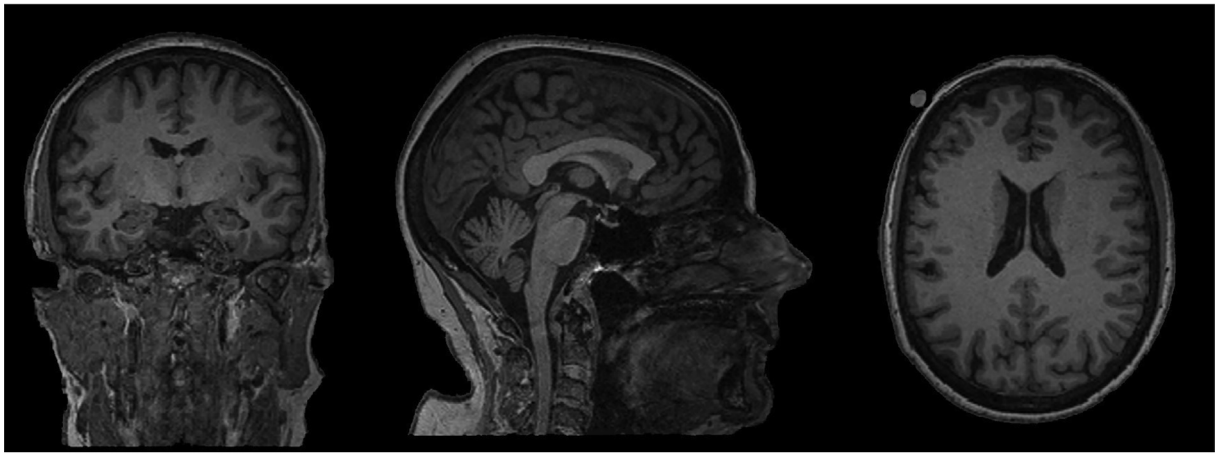
Only 3 out of 4 patients have a T_2-weighted sequence in the sample data. We will subset those patients' covariates and the preprocessed image paths to execute the RAVEL algorithm.

```
## Defining the RAVEL output files for the patients
  ## with a T2-weighted sequence (patient 1,2 and 4)
patients <- c(1,2,4)
output_files <- lapply(patients, function(x)
  {file.path(folder, paste0("patient0",x),
  "T2_ravel.nii.gz")})
## Getting the files of the preprocessed images
```

(continued on next page)



(a) Preprocessed MRI scan



(b) Raw MRI scan

Fig. 3. Sagittal, axial, and coronal slice views of preprocessed and raw T_1-weighted scan of the same patient. Significant changes can be appreciated from (b) to (a). The MRI scan has been cleaned and standardized, and it is ready for further analysis.

```
  (without intensity normalization)
## and the CSF masks computed by the preprocessing.
csf_paths <- lapply(paths_preprocess_patients
  [patients], function(x)x$csf_mask)
masked_paths <- lapply(paths_preprocess_patients
  [patients], function(x)x$stripped[2])
## Subseting covariates info
cov_pat <- clinical_info[clinical_info$patient ##
  Applying RAVEL to T2 sequences
image_normalization_ravel(masked.paths
  = masked_paths, csf.paths = csf_paths,
  ravel.paths = output_files, demographics
  = cov_pat, brain.mask = atlas_mask,
  patients.folder = folder, modality = "T2")
```

4. Validation

4.1. Data sets

`NeuroNorm` has been evaluated using the T_1-weighted, T_2-weighted, and FLAIR MRI scans from three different studies. The first study corresponds to the Alzheimer's Disease Neuroimaging Initiative (ADNI). The data set available for testing our pipeline comprises a subset from the ADNI 3 cohort of the ADNI study. The data set consists of MRI scans from 60 Alzheimer's, 30 Mild cognitive impartment, and 75 healthy subjects (normal controls). The data also includes patient-specific covariates such as sex and age. The second dataset was obtained from the Parkinson's Progression Markers Initiative (PPMI) study [32]. The selected dataset is conformed by 60 Parkinson's patients and 75 Healthy subjects' MRI scans and clinical data. The clinical data refers to the sex and age of the patients. The third data source is the University Medical Center Ljubljana (UMCL) which disseminated a public MS dataset of 30 Multiple Sclerosis patients, including MR images and biological data [33]. The publicly available dataset was created to encourage further use and research in MS lesions segmentation. We used the entire dataset from 30 patients comprising 3D T_1-weighted scans and biological data such as sex and age of the study participants.

4.2. Results

We preprocessed 330 T_1-weighted, 300 T_2-weighted and 30 FLAIR images from 330 subjects by using the `preprocess_patients()` function in the `NeuroNorm` package. We used a computer with 8 GB of RAM and Intel Core i5. The average computational time of preprocessing a patient's MRI data took 6 to 8 min, depending on the patient's available MRI sequences.

Fig. 4 shows preprocessed T_1-weighted scans of five subjects. The raw images came from three different sources with specific parameters on image dimensions, voxel intensity ranges, patients characteristics, acquisition protocols and scanner types. It is evident how the preprocessed images can be constrained each other

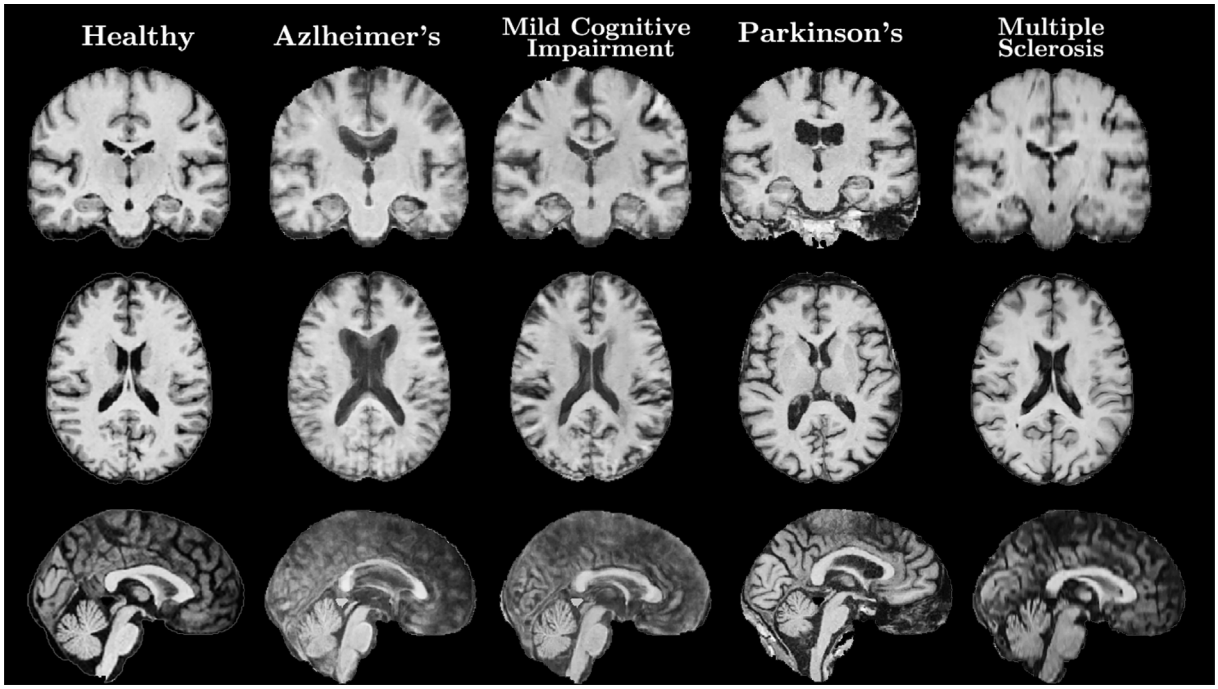


Fig. 4. Sagittal, coronal, and axial slice views of preprocessed T_1-weighted scans of a healthy individual and four patients with distinct neurodegenerative diseases: Alzheimer's disease, Mild cognitive impairment, Parkinson's disease, and Multiple Sclerosis.

because they shared the same geometrical space and intensity range. Moreover, biological markers associated to neurodegenerative diseases such as the medial temporal lobe atrophy in Alzheimer's and Mild cognitive impairment, the substantia nigra regions in Parkinson's and, the white matter lesions in Multiple Sclerosis are preserved. This occurs because of the preprocessing algorithms selected for the `NeuroNorm` preprocessing pipeline. `NeuroNorm` normalized and denoised the MRI scans without compromising biological information, thus ensuring comparability between subjects.

The preprocessed MRI scans will increase the sensitivity of any analysis and certify the validity of any model that uses them. `NeuroNorm` outcome data can be employed in further analysis, for instance, disease classification analysis, region volume estimation or feature extraction. `NeuroNorm` was successfully applied to preprocess MRI images in order to detect and classified neurodegenerative diseases [34].

5. Discussion and conclusions

`NeuroNorm` is a structural MRI preprocessing pipeline characterized by its robustness, manipulability and flexibility. It also produces highly specified and coherent results. We demonstrated how using state-of-the-art preprocessing methods, and a flexible configuration allows the workflow to adapt to multiple inputs. It automates the adaptation to the input information and assures the quality of results. Our workflow integrates and simplifies well-known neuroimaging software packages. `NeuroNorm` pipeline is easy to use for neurologists, physicians, and medical researchers with essential programming experience. We showed how our workflow requires minimal user inputs and interaction and produces valuable MRI information. We also validated the robustness of our pipeline on numerous MRI data from datasets associated with different studies. By visual inspection, we found that our results exhibit high-quality standards and preserve patients' biological characteristics.

`NeuroNorm`, as an integrated R package, distinguishes itself from individual software tools such as FreeSurfer, FSL, ANTs, and Insight Toolkit by offering a more comprehensive and user-friendly approach to neuroimaging preprocessing. While each of these tools focuses on specific aspects of preprocessing, `NeuroNorm` consolidates and harmonizes their functionalities into a unified pipeline. This integration not only improves the efficiency and usability of the preprocessing workflow, but also expands the range of capabilities available to researchers. `NeuroNorm` goes beyond simply incorporating the core preprocessing algorithms from these established software tools. It also introduces additional features and enhancements that cater to the challenges posed by large datasets obtained from diverse sources. By providing a holistic solution that combines the strengths of multiple tools, `NeuroNorm` offers a valuable resource for researchers seeking a comprehensive and efficient preprocessing framework.

One limitation of this work relates to the algorithms and methods implemented in the pipeline. Although many alternatives for each step exist, they are used in precise settings and analysis and are rare in neuroimaging research. `NeuroNorm` adopts forefront techniques to facilitate data integration and further analysis. `NeuroNorm` pipeline is also restricted to the Neuroimaging Informatics Technology Initiative (NIfTI) since it is the preeminent format in neuroimaging analysis studies. Likewise, our workflow does not support MRI data from rodents and nonhuman primates. `Neuronorm` only preprocesses MRI scans from humans. Future work will focus on integrating other preprocessing techniques and formats.

The interpretation of MRI outputs processed by `NeuroNorm` requires careful consideration due to the inherent limitations of the methods incorporated in its pipeline. An important aspect to address is the choice of template for spatial registration, as an inappropriate selection can introduce distortions in anatomical structures, thereby hindering meaningful comparisons between subjects or studies [35]. Therefore, it is crucial to carefully evaluate and select a template that accurately represents the population under investigation, ensuring reliable anatomical alignment across

MRI scans. While NeuroNorm defaults to the MNI template, users have the flexibility to choose an alternative template that aligns with the specific requirements of their study. Another limitation arises from the HMRF segmentation method deployed in NeuroNorm. In cases where low-resolution MRI scans are provided, the HMRF algorithm may encounter challenges in identifying appropriate thresholds for classifying gray matter and white matter, potentially resulting in misclassification [30]. To address this, we recommend researchers visually inspect the segmentation outputs to assess their consistency and consider employing alternative validation methods if deemed necessary. Furthermore, attention must be given to the intensity normalization step in NeuroNorm. The RAVEL method utilized in this process relies on the accuracy of the tissue segmentation results. In cases where the segmentation yields incorrect results, the RAVEL algorithm may remove relevant biological signals or associate control regions with the outcome under investigation [16]. To mitigate this limitation, researchers are advised to exercise caution and thoroughly assess the segmentation results to ensure the preservation of meaningful information. We suggest users verify the preprocessed MRIs for a random selection of patients from each MRI dataset, enabling an evaluation of the segmentation quality and aiding in the identification of potential inconsistencies or errors.

The NeuroNorm R package is available at CRANhttps://cran.rstudio.com/web/packages/neuronorm or in Neuronorm GitHub repository. Considering the increasing studies comprising structural MRI data [10], NeuroNorm aims to better support structural MRI practitioners in performing reproducible analyses with a high-quality, adaptive, and practical preprocessing tool.

CRediT authorship contribution statement

David Payares-Garcia: Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Data curation, Visualization, Writing - original draft. **Jorge Mateu:** Investigation, Validation, Supervision, Writing - review & editing. **Wiebke Schick:** Supervision.

Data availability

The authors do not have permission to share data.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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