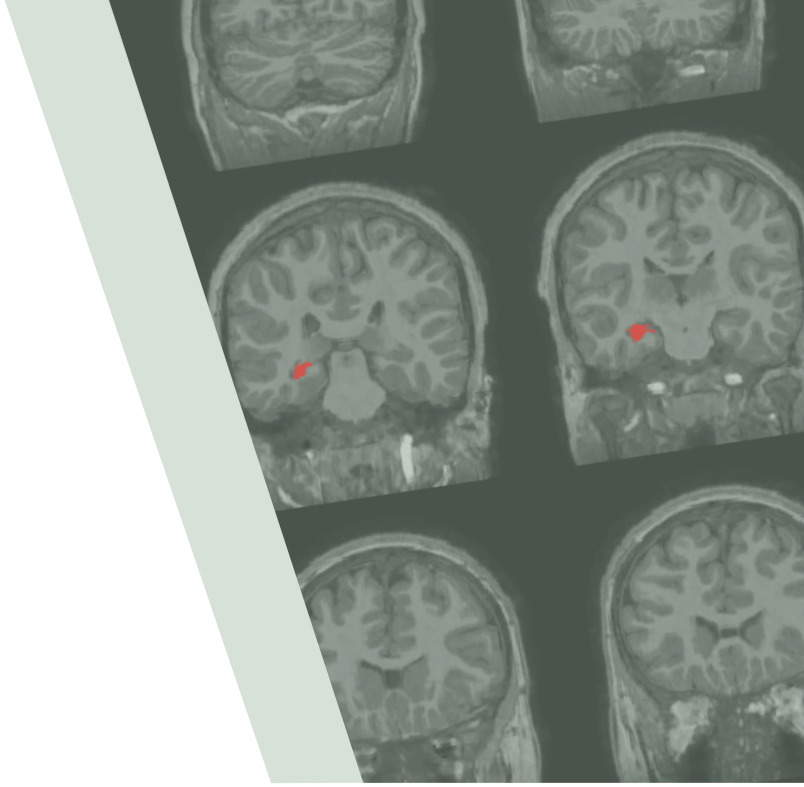
Neurocloud-VOL

Volumetric analysis for atrophy and lesion quantification in MRI

QUBIO tech

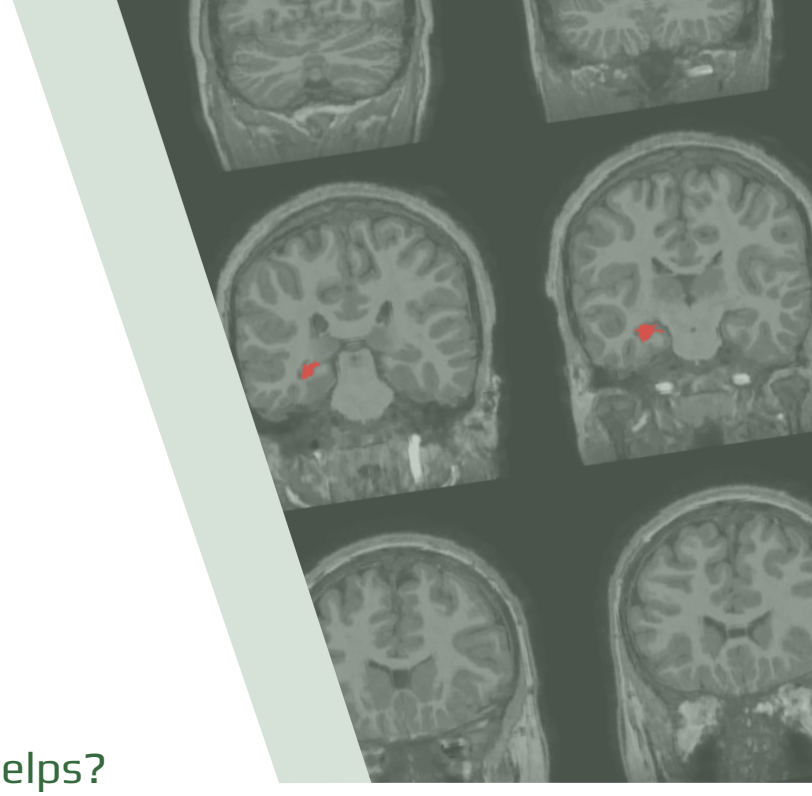


01 What is **Neurocloud-VOL**?

Neurocloud-VOL is a CE marked software for the automatic analysis of Magnetic Resonance images (MRI) of the brain. Through an easy-to-use web-based interface, the qualified user can upload neuroimages in the standard DICOM format and obtain valuable information with just one click of intervention. In a few minutes, the user can review the results in the specific analysis dashboard, showing both visual and quantitative data. The system also allows for downloading a customizable report of findings and navigating through different quantification overlays superimposed over the patient MRI with our 3D online viewer. All the relevant image, tabulated and graphical data provided by Neurocloud-VOL can be downloaded in DICOM format as well.

Neurocloud-VOL is designed to aid physicians along the different stages in the evaluation of patients suffering from neurological conditions; at the initial visit for diagnosis assessment assistance, in monitoring disease progression, and also in the therapeutic planning. Neurocloud-VOL can detect abnormalities that are pathological manifestations revealed in T1-weighted MRI by segmenting cortical, subcortical and other brain structures of clinical relevance and by comparing volumetric data in patient's brain with the normality distribution derived from a large database of healthy controls. Neurocloud-VOL can also identify and label inflammatory lesions appearing in T2-FLAIR MRI as hyperintense regions in the white matter tissue surrounding the ventricles, which are the pathologic hallmark in Multiple Sclerosis.

The physician/radiologist can use the information provided by Neurocloud-VOL to validate his/her findings from the visual examination of MRI and complement them with unbiased quantitative and less rater-dependent data for achieving a more robust evaluation and reducing the diagnostic errors rate. This white paper aims to describe how Neurocloud VOL works and how it can help in the clinical routine. The methodologies it uses, the information it provides to the user and the reliability of its performance are detailed.



02 How **Neurocloud-VOL** helps?

In the examination of patients manifesting neurological symptoms or, after diagnosis assessment, to study disease progression, the clinical guides recommend the use of non-invasive MRI studies to look for abnormalities in the brain. The traditional approach is to handwrite a report with the relevant findings from the visual inspection of the neuroimages, which is a highly specialized and time consuming labor that, moreover, only provides qualitative data that is prone to inter-rater and intra-rater variability.

Neurocloud-VOL software, on the other hand, produces objective data in an automatic manner and within reduced times. The specialist can use the clinically oriented report for confirming or reviewing the results of the initial visual exam, and use the quantitative data for a more robust estimation of the impact and evolution of the disease.

The software follows a generalist approach which allows it helping in the diagnosis of different neurological conditions by revealing their particular patterns of abnormalities (Figure 1), for instance:

- Alzheimer disease (AD): in the evaluation of AD's patients temporal atrophy is usually observed, primarily on the medial section of the temporal lobe and affecting structures like the hippocampus or the entorhinal cortex [1].
- Fronto-temporal dementia: patients manifesting these conditions generally present atrophy involving frontal structures, such as the orbitofrontal and anterior cingulate regions, or the Insula [2].
- Multiple sclerosis: reduced brain parenchymal fraction and tissue loss in internal brain structures (putamen, thalami or cerebellum) and, in the white matter tissue surrounding the ventricles, inflammatory lesions appear as hyperintense signals in T2-FLAIR sequences [3].
- Temporal lobe epilepsy: hippocampal atrophy is the main feature of this condition [4].

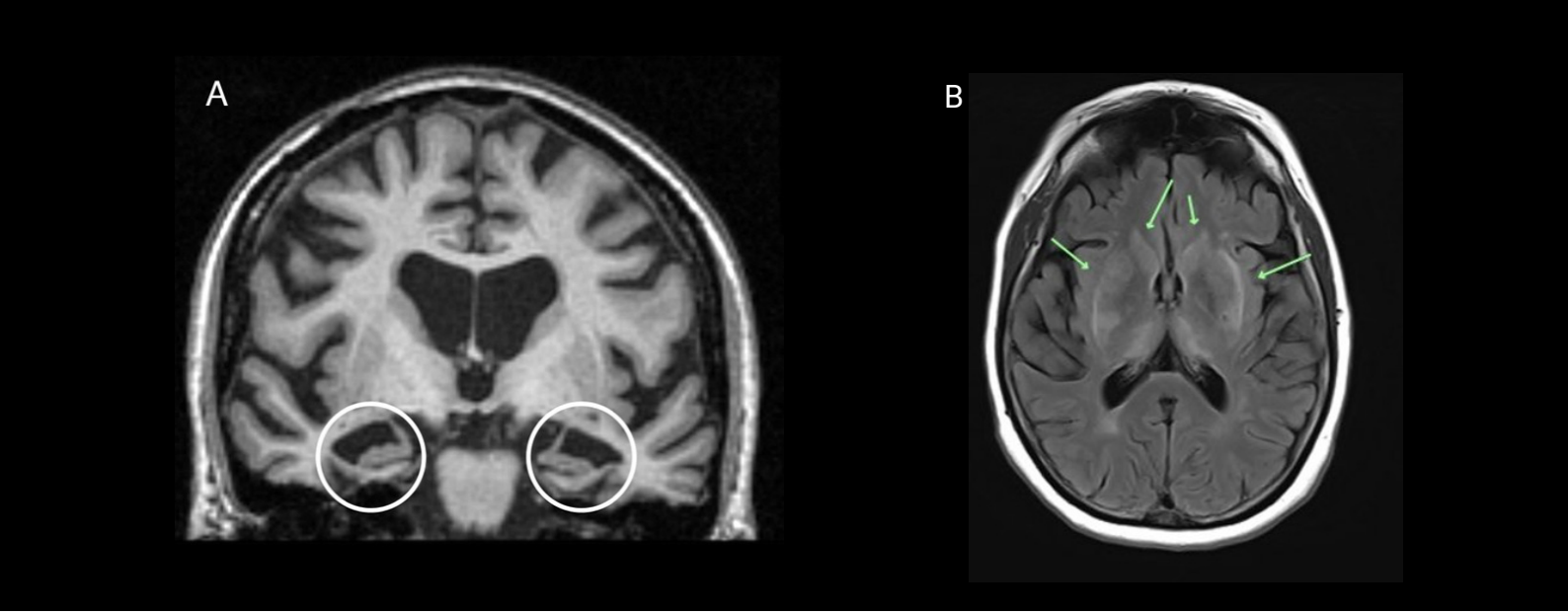


Figure 1: Coronal 2D slice from a 3D T1 weighted MRI (left) showing symmetrical medial temporal lobe atrophy (circled) in postmortem proven Alzheimer's disease [5]. T2- FLAIR MRI axial slice (right) showing the hyperintense abnormalities (arrows) that are the main pathological characteristic in Multiple Sclerosis [6]

03 How **Neurocloud-VOL** works?

Neurocloud-VOL implements state-of-the-art methods for segmentation of imaging features of clinical relevance. This section presents technical information regarding the methodologies employed in the image analysis pipeline that are dependent on the type of MRI sequence provided.

1. T1-weighted MRI analysis

For the volumetric study of T1-weighted sequences, the main procedure is the brain data segmentation in three major tissue classes; Gray Matter (GM), White Matter (WM) and Cerebrospinal Fluid (CSF) (Figure 2). For this, an adaptive technique is used where local variations of the intensity parameters (means and variance) are modelled as slowly varying spatial functions [7] to account for inhomogeneities and other local intensity variations. Tissue class probability maps (TPM) are employed during the process, but just for spatial normalization, initial skull-stripping, and to obtain the starting segmentation estimates. For more robust results, two image denoising methods are applied; 1) the Spatial-Adaptive Non-Local Means filter, allowing to maintain edges in the image [8], 2) a classical Markov Random Field approach, which includes spatial information from adjacent voxels in the segmentation estimation. Furthermore, a local intensity transformation of all tissue classes is used to reduce the effect of intensity variations that different acquisition protocols may induce at different brain regions, and, finally, a partial volume correction is applied based on a simplified mixed model of a maximum of two tissue types [9].

During the segmentation process, the MRI is spatially normalized to the MNI standard space using DARTEL [10] for proper use of TPM information and for a reliable analytic comparison with the database from healthy controls (see corresponding section). The spatial transformations applied result in a deformation field map that describes how local structures were adjusted to match different brains to each other. These fields can be used to correct segmentations for volume changes so the amount of original matter is preserved, and to use anatomical parcellation maps (brain atlases) for cortical and subcortical structures labelling, as it is required for the posterior volumetric analysis.

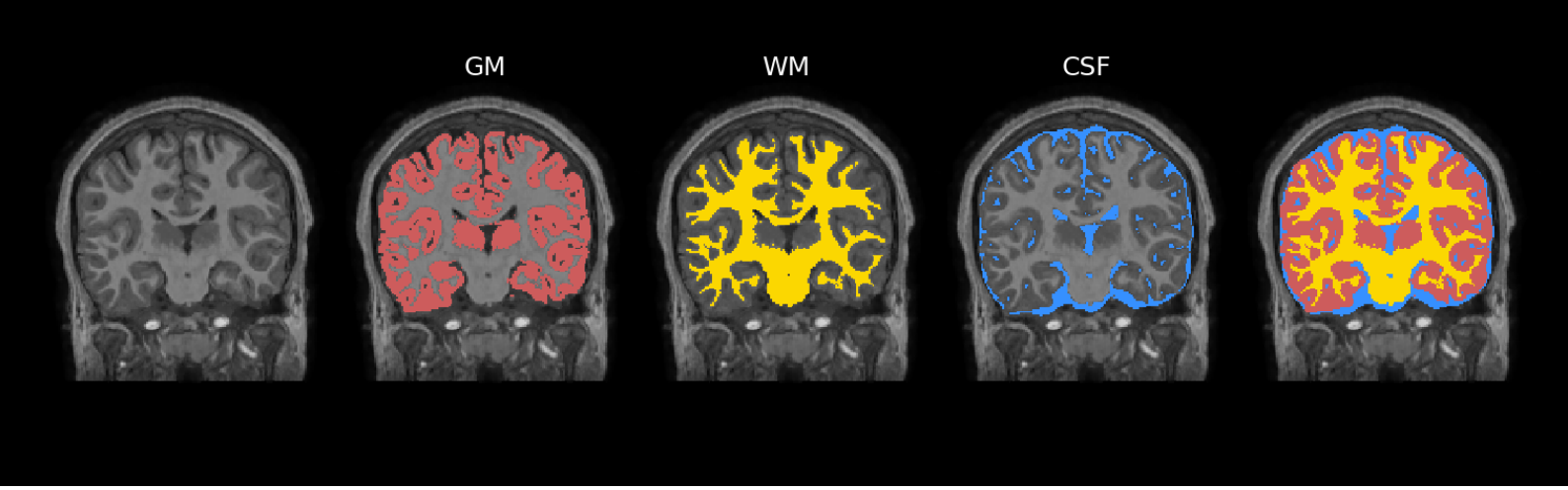


Figure 2: An example of the results obtained with Neurocloud-VOL on the brain segmentation in GM, WM and CSF tissues from T1-weighted MRI.

2. T2-FLAIR MRI analysis

By applying some of the procedures just described, the T2-FLAIR image follows tissue segmentation and standard space normalization. The resulting segmentation maps are used to remove non-lesion voxels by subtracting the mean of standardized GM voxels from T2-FLAIR intensities and subsequently applying a WM mask. The outcome of this thresholding step is a lesion probability map containing lesion candidates. This data is used as input for a pre-trained binary regression model [11] that finally classifies the image voxels in lesion and non-lesion voxels.

Note that when a T1-weighted MRI is also included in the analysis (recommended), co-registration of both sequences takes place before normalization. The use of T1-weighted data allows also for a more robust segmentation in tissue classes and for achieving an optimal registration with images in native space, as needed for registration with predefined masks in MNI space that are used for classifying lesions following a standard criteria [12].

04 What information **Neurocloud-VOL** provides?

The basic outcomes from an MRI analysis with Neurocloud-VOL are segmentation maps for brain structures and other imaging features of clinical interest plus the associated volumetric data. These data can be used for a quantitative-driven study of disease status and progression and are mandatory to conduct analytic comparison of measures in the patient's brain with normality intervals (5-95 CL) derived from healthy controls. With this regard, age and morphological differences among brains are taken into account when constructing the normality intervals, as it is required for a reliable comparison.

Atrophy is evaluated based on T1-weighted data and using different biomarkers and methods (Figure 3, 4):

- **Global analysis:** the Brain Parenchymal Fraction (BPF) and the Gray Matter Parenchymal Fraction (GMPF) [13], calculated by normalizing the sum of GM and WM volumes to the total intracranial volume (TIV), or just the amount of GM for the latter magnitude, are good biomarquers of generalized atrophy.
- **Asymmetry analysis:** volume in contralateral ROIs is used to compute an asymmetry index for each structure, a relevant metric to evaluate alzheimers and epilepsy patients [14] [15].
- **ROI-based analysis:** volume at each ROI is compared with normality intervals and considered abnormal when yields outside the 5-95 CL interval, these results are important to discover the characteristic patterns of diseases like Alzheimer's and other dementias and MS.
- **Voxel-based analysis:** following a voxel-level morphometry approach [16] more subtle tissue losses, that can easily go unnoticed, are revealed. This study provided also with results that complement and generally support the findings of the classical ROIs-based exploration.

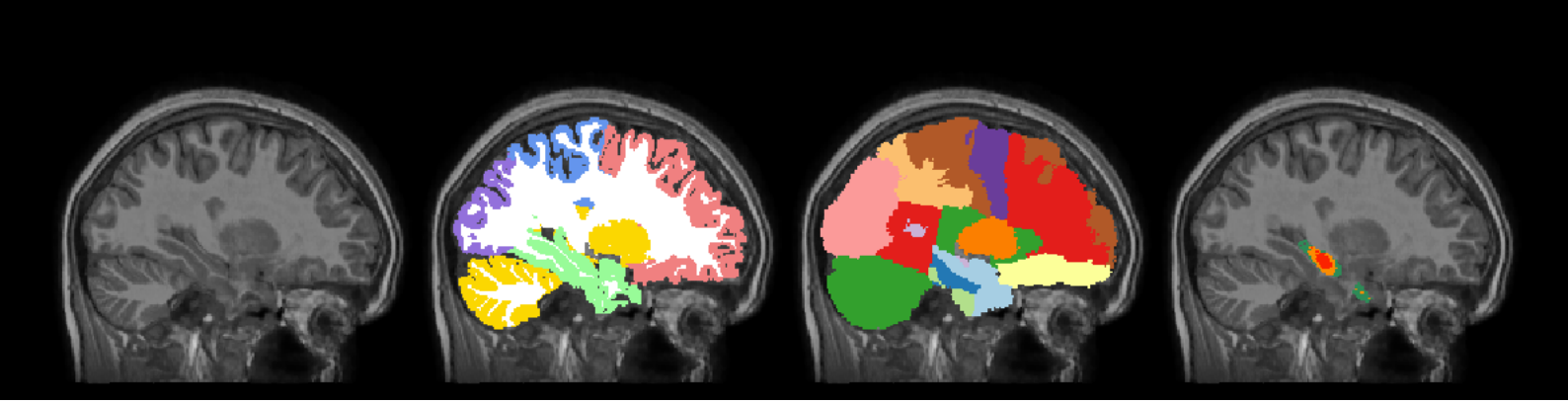


Figure 3: Sagittal slice of a T1-weighted MRI from a TLE patient with segmentation, ROIs and atrophy maps (left to right) as presented by Neurocloud-VOL

Temporal −

	ROI	Left hemisphere GM [%TIV] (5% - 95%)	Right hemisphere GM [%TIV] (5% - 95%)	Asymmetries [%]	Laterality
	Amigdala	0.14 (0.10 - 0.13)	0.13 (0.11 - 0.14)	7.41	Right
	Hippocampus	0.16 (0.13 - 0.17)	0.12 (0.14 - 0.18)	28.57	Right
	Parahippocampal and ambient gyri	0.27 (0.19 - 0.25)	0.24 (0.20 - 0.25)	11.76	Right
	Anterior temporal lobe, medial part	0.41 (0.29 - 0.39)	0.32 (0.30 - 0.38)	24.66	Right
	Anterior temporal lobe, lateral part	0.57 (0.37 - 0.47)	0.40 (0.33 - 0.43)	35.05	Right

Figure 4. Neurocloud - VOL quantification data indicating hippocampal atrophy in a TLE patient.

Using T2-FLAIR data Neurocloud-VOL can provide both visual and quantitative information enabling a comprehensive inflammatory lesions characterization (figures 5, 6) :

- **Lesion segmentation:** algorithm can detect and size inflammatory lesions with a minimum volume of 15 microlitres and classify them with a color code for an easy review in axial, coronal and sagittal views.
- **Volumetrics:** total lesion load is given in cm^3 together with the number of isolated clusters detected.
- **Classification:** following a clinical criteria [18] (validated in clinical environment), lesions are labelled as periventricular, infratentorial, juxtacortical or deep white matter lesions.

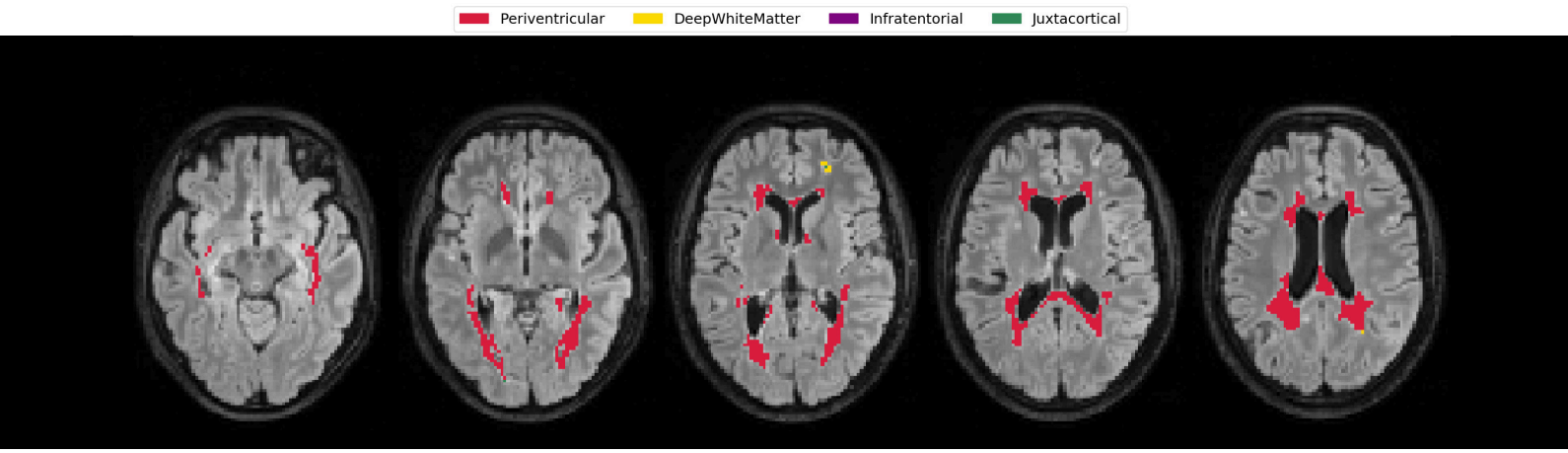


Figure 5: Axial slices for a T2-FLAIR image from a MS patient with lesion maps in color code as presented by Neurocloud-VOL.

CLASSIFICATION		
Region	**Lesions**	**Volume [cm3]**
Periventricular	14	25.23
Deep white matter	11	2.83
Infratentorial	0	0
Juxtacortical	0	0
Total	25	28.06

Figure 6. Classification and quantification of white matter lesions in a Multiple Sclerosis study presented by Neurocloud-VOL

All the data provided automatically by our software can be reviewed in the analysis dashboard where it is presented in an easy to read structure . Imaging results can be displayed using the 3D online viewer and downloaded in DICOM (or NifTi) format, along with tabulated data and other graphical elements used for better readability of the results. Moreover, a customizable report of findings can be obtained in PDF and DICOM formats.

05 How **Neurocloud-VOL** performs?

To evaluate the performance of Neurocloud VOL software for atrophy quantification several tests were conducted using a variety of publicly available T1w imaging datasets ([19], [20], [21], [22], 23]) summing up more than one thousand volumes covering a wide age range, different pathologies spectrum and scanners models (1.5T to 3T) from the main manufacturers. These tests included, among others, accuracy evaluation studies against manual annotations from experienced radiologists and against a volumetry reference software (Freesurfer), and also reproducibility analysis on test-retest data. The complete results of this evaluation were presented to the spanish neuroradiology community during the SENR 2018 meeting [24]. All the evaluations carried out verified the expected performance for Neurocloud-VOL showing strong correlation with human experts measurements data.

Hippocampal segmentation Expert annotations vs Neurocloud-VOL					
Metrics: Pearson's R, Intra-class correlation coefficient and Volume difference					
Left Hemisphere			**Right Hemisphere**		
R (95%CI, p-value)	**ICC (3,1) (95%CI)**	**V diff**	**R (5-95, p-value)**	**ICC (3,1)**	**V diff**
0.90 (0.87-0.93, <0.001)	0.81 (0.74 - 0.86)	< 0.07	0.89 (0.84-0.92, <0.001)	0.82 (0.75 - 0.87)	< 0.06

Table 1: Hippocampal segmentation accuracy tests results comparing Neurocloud-VOL against human expert annotations on 135 manual annotated images from the ADNI project [19] [20].

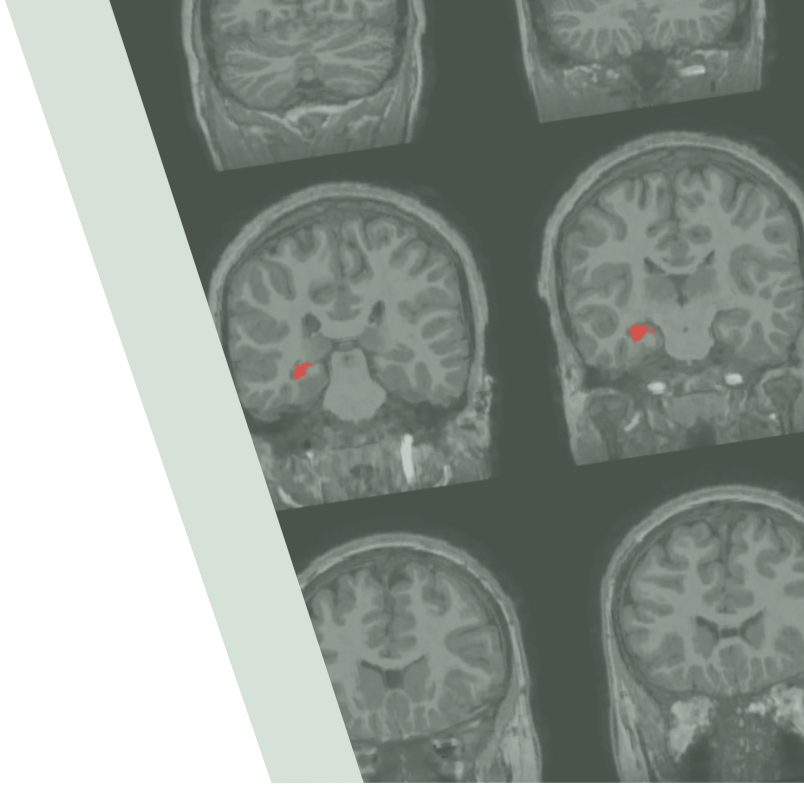
Hippocampal segmentation				
Test-Retest				
	Left Hemisphere		Right Hemisphere	
	A-B Mean (STD)	Coefficient of variation RMS	A-B Mean (STD)	Coefficient of variation RMS
Neurocloud-VOL	2.25 (0.21) - 2.24 (0.21)	1.36	2.39 (0.22) - 2.38 (0.22)	1.1
Freesurfer	4.08 (0.37) - 4.09 (0.41)	2.81	4.23 (0.40) - 4.23 (0.40)	2.53

Table 2: Performance of Neurocloud-VOL versus FreeSurfer for hippocampal segmentation in test-retest experiments using 40 T1w volumes from 20 different subjects scanned in two consecutive sessions [23].

Performance evaluation of the Neurocloud-VOL software for white matter lesions segmentation from FLAIR sequences was done using open-source access datasets ([22], [24], [25])summing up more than 300 volumes acquired with 1.5T and 3T MRI scanners. These datasets included participants between 19 and 65 years old, the majority of whom were patients previously diagnosed of Multiple Sclerosis. Each FLAIR volume here was linked to the corresponding consensus mask image of the complete white matter lesion segmented by one or more radiology specialists. The total volume values from manually segmented lesions were put in comparison against those obtained by using Neurocloud-VOL. As shown in Table 3, both measurements correlate highly, supporting the automatic segmentation achieved by this software in terms of accuracy.

Lesion segmentation in FLAIR	
Manual segmentation vs Neurocloud-VOL	
Pearson's R	ICC
0.91	0.87

Table 3: Performance of Neurocloud-VOL for white matter lesions segmentation against experts manual segmentations of consensus.



05 Neurocloud-VOL database

The Neurocloud-VOL database contains data from more than 800 T1-weighted images acquired on volunteers with no history of neurological disorders. MRI scans were obtained using 1.5T and 3.0T machines from the three major vendors (Philips, GE and Siemens). Participants were interviewed for cognitive status assessment based on the Clinical Dementia Rating or the MMSE scores. All this imaging data was processed with Neurocloud-VOL and one-versus-all statistical analyses were done to reject scans deviating significantly from the normality to compose the final controls database. Table 4 and Figure 7 summarize some basic aspects of the final cohort.

	Total	Males	Females
Number	852	375	Female
Age range (mean +/- std)	19 - 94 (57.8 +/- 18.8)	20 - 90 (56.3 +/- 19.3)	20 - 94 (59.1 +/- 18.3)

Table 4: Basic demographic data from the Neurocloud-VOL controls database.

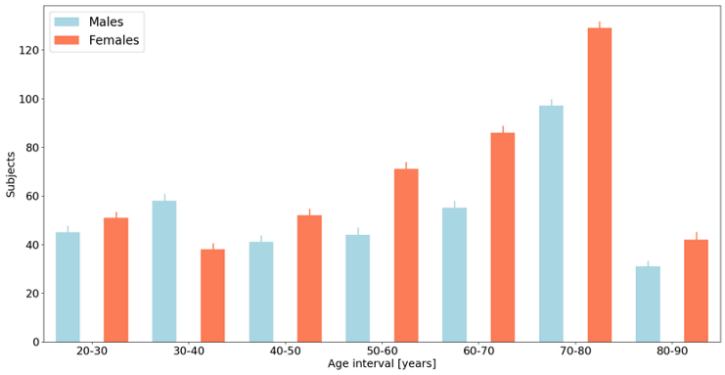


Figure 6: Distribution in age ranges of healthy controls in the Neurocloud-VOL database.

Features

- Sensitive. Identifying atrophic VOIs in the early stages of the disease thanks to one of the most extensive normal bases on the market, which is also stratified by age.
- Specific. Providing quantitative information on the volume of VOIs, and their deviation from normality and voxel-based morphometric patterns.
- Objective.Reducing inter-observer variability among specialists.
- Quickly. Results are available in 10 minutes. In addition, it integrates all the resources needed for diagnosis: medical images and patient report history.

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