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High-resolution atlasing and segmentation of the subcortex: Review and perspective on challenges and opportunities created by machine learning

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ABSTRACT

This paper reviews almost three decades of work on atlasing and segmentation methods for subcortical structures in human brain MRI. In writing this survey, we have three distinct aims. First, to document the evolution of digital subcortical atlases of the human brain, from the early MRI templates published in the nineties, to the complex multi-modal atlases at the subregion level that are available today. Second, to provide a detailed record of related efforts in the automated segmentation front, from earlier atlas-based methods to modern machine learning approaches. And third, to present a perspective on the future of high-resolution atlasing and segmentation of subcortical structures in *in vivo* human brain MRI, including open challenges and opportunities created by recent developments in machine learning.

1. Introduction

The cerebral cortex is the outermost layer of tissue of the cerebrum and comprises almost half of its mass. The cortex is the main information-processing centre of the brain, and is involved in crucial functions such sensing, motor tasks, or language. The subcortex, on the other hand, comprises a number of non-cortical grey matter structures, and is responsible for generally more primitive functions, such as memory or emotion.

Historically, the majority of studies of brain anatomy and function have focused on the cortex, due to its involvement in higher order functions. Even today, some high-profile atlasing efforts are exclusively focused on cortical regions (e.g., Glasser et al. 2016). Nevertheless, the last two decades have seen a large increase in the number of studies focused on the subcortex, enabled by advances in MRI and other neuroimaging modalities, as well as image analysis techniques.

Due to their different geometry, the cortex and subcortex have been studied with different types of computational methods. With some exceptions (e.g., Shattuck et al. 2008), modern cortical analysis is dominated by 2D methods operating on the surface domain. Such surface-based techniques are best represented by the routines implemented in the open-source package FreeSurfer (Dale et al., 1999; Fischl et al., 1999a; 2004). These methods account for the convoluted shape of the cortex, preventing "leakage" between points that are close in 3D but far away on the cortical surface (e.g., across a sulcus), and thus yielding much higher localisation accuracy of structural and functional features (Fischl et al., 1999b).

On the other hand, subcortical analysis largely relies on volumetric atlases and image processing techniques. Subcortical atlases are almost always defined on regular (and often Cartesian) 3D grids, e.g., Evans et al. (1993),Mazziotta et al. (2001), Shattuck et al. (2008), Fischl et al. (2002) and Ashburner and Friston (2005). Similarly, analysis methods are also defined on such grids, e.g., image segmentation and registration methods, implemented both with classical (Ashburner and Friston, 2005; Fischl et al., 2002; Iglesias and Sabuncu, 2015; Sotiras et al., 2013; Van Leemput et al., 1999; Wells et al., 1996) and deep machine learning (ML) techniques (Balakrishnan et al., 2019; Henschel et al., 2020; Kushibar et al., 2018; Roy et al., 2018; de Vos et al., 2019). Initial efforts to build electronic atlases of the human brain were based on digitising printed versions (e.g., Nowinski 2005). These early atlases were superseded by 3D atlases derived from volumetric images, which are better suited for *in vivo* segmentation of brain MRI. More recently, with the advent of 3D histology (Pichat et al., 2018), there have been new efforts to build 3D atlases from histology (Amunts et al., 2013; Ding et al., 2016).

While the ultimate goal of the techniques surveyed in this article is to study subcortical regions of interest (ROIs) in *in vivo* MRI scans, such methods can rely on training data derived from brain images acquired *in vivo* or *ex vivo*. Using *in vivo* imaging with MRI enables building atlases

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and segmentation methods with no domain gap, since the modalities of the training and test data can be approximately matched, e.g., by using T1-weighted scans with 1 mm isotropic resolution. While this approach yields atlases with highly representative intensities and accurate segmentation methods, it also has the disadvantage that it cannot model smaller ROIs (Keuken et al., 2018). This is due to limitations of *in vivo* scanning in terms of resolution and signal-to-noise ratio, which lead to nearly indistinguishable inter-regional boundaries, and hamper the definition of delineation protocols.

Ex vivo imaging techniques, on the other hand, enable atlasing of small ROIs that are not easily discernible *in vivo* with MRI. For example, *ex vivo* MRI does not suffer from motion artefacts, which enables very long acquisitions and thus very high resolutions. Another example is histology, which has extremely high resolution in plane, and capitalises on a wide array of stains that highlight different microscopic features of brain tissue. The main disadvantage of these images is that their contrast and resolution are very different from those found in the *in vivo* MRI scans that one ultimately wishes to analyse. These differences create a large domain gap that is detrimental in image analysis. For example, deformable image registration across contrasts is substantially less accurate than within modalities (Iglesias et al., 2013). Another example is segmentation with deep ML techniques: even with advanced domain adaptation techniques (Wang and Deng, 2018; Wilson and Cook, 2020), it would be nearly impossible to train a deep neural network on, e.g., histology, and successfully apply it to the segmentation of *in vivo* MRI. However, this limitation can be circumvented by Bayesian techniques (Ashburner and Friston, 2005; Van Leemput et al., 1999), which decouple the models of anatomy and image formation: the former is independent of modality, and can be learned from the high-resolution scans (typically in the form of a probabilistic atlas); the latter is typically modelled with a Gaussian mixture, whose parameters are fitted to the MRI scan to segment.

Precise characterisation of subcortical regions *in vivo* has important clinical and research applications. In the clinic, it enables the development of new anatomical targets, e.g., more specific cortical-subcortical brain circuits in epilepsy treatments (He et al., 2020), or more accurate MRI-informed placement of the electrodes in deep brain stimulation (DBS) for patients with Parkinsons's disease (Ineichen et al., 2018). In research, such improved characterisation has the potential to unveil new imaging biomarkers for disease progression modelling or diagnosis (Veldsman et al., 2021), or to facilitate the development of new theories and hypothesis to be tested with neurocomputational models (Bogacz and Gurney, 2007).

High-resolution atlases, ML algorithms, and the advent of data-sharing initiatives (e.g., Alkemade et al. 2020) create opportunities to develop robust, well-validated segmentation algorithms that will undoubtedly favour the exploration of the subcortex. By high-resolution we refer to sub-mm resolution needed to target subcortical nuclei, either with gold-standard 3D histology reconstruction or improved MRI sequences (typically *ex vivo*). In this manuscript, we first survey the existing literature of atlasing and segmentation methods for subcortical brain imaging, and then discuss the challenges associated with these next-generation, high-resolution techniques. It is not the goal of this article to provide an exhaustive account of atlasing and segmentation efforts for the past three decades; we acknowledge that works that would be considered important by some readers may have been omitted (e.g., connectivity-based techniques). Instead, we sought to generally cover the wide variety of literature on atlases and segmentation methods, in order to set the field for discussion of challenges and opportunities of machine learning for *in vivo* MRI segmentation of subcortical nuclei using high-resolution atlases. For a historical review of the evolution of human brain atlases, we refer the reader to Nowinski (2021). A complete characterisation of the human brain anatomy can be found e.g., in the Atlas of the Human Brain by Mai et al. (2015)); it features different aspects of brain morphology and topography at microscopic and macroscopic levels. Finally, other brain regions (cerebellum and brain stem) have also been well studied in the literature (e.g., Naidich et al. (2009)), but fall out of the scope of this article. The rest of this article is organised as follows. Section 2 surveys atlases of subcortical structures in the human brain. Section 3 reviews automated segmentation methods – most of which are based on the atlases of the previous section, combined with image registration and ML techniques. In Section 4, we discuss some of the challenges and potential solutions for *in vivo* segmentation using ML. Finally, Section 5 concludes the paper. The subcortical structure acronyms used throughout the manuscript are listed in Table 1.

Table 1
List of abbreviated subcortical structures.

CAU	Caudate
PU	Putamen
AM	Amygdala
TH	Thalamus
PA	Pallidum
NA	Nucleus accumbens
HTh	Hypothalamus
SN	Substantia nigra
BF	Basal forebrain
HP	Hippocampus
STN	Subthalamic nucleus
ST	Striatum
ZI	Zona incerta
AC	Anterior commissure
VTA	Ventral tegmental area
SepN	Septal nuclei
CL	Claustrum
Fx	Fornix
PAG	Periaqueductal gray
PPN	Pedunculopontine nucleus
IC	Internal capsule

2. Subcortical brain atlases

2.1. Types of atlases

Three-dimensional human brain atlases are volumetric datasets that encode knowledge on the anatomy of this organ, in terms of semantic labels (corresponding to brain structures or tissue types), image intensities of a given modality (typically MRI of a specific contrast, e.g., T1), or both. Atlases are of paramount importance in brain mapping, as they provide reference spaces for analysing intra-population variability, group studies, functional analysis, and image segmentation. In this section, we review the different types of volumetric atlases, typically built from MRI or 3D histology reconstruction, that are most often used to model the subcortex; a discussion on cortical atlases – often parameterised on surfaces – is out of the scope of this article and can be found elsewhere.

Atlases based solely on intensities are often known as "templates". In their simplest form, they consist of the image intensities of a single case (e.g., Holmes et al. 1998). Using a subject's MRI as template enables the spatial normalisation required by many analyses, but has the disadvantage of being biased towards the chosen subject. For this reason, $N = 1$ templates are currently used only when data acquisition is highly expensive. Notable examples include the ultra-high resolution BigBrain (Amunts et al., 2013) or the Allen Institute atlas (Ding et al., 2016), both built from histology. More representative templates can be built with a larger number of subjects, typically via co-registration and averaging of their imaging data. The co-registration procedure is often iterative, and all input images must be treated equally in order to avoid biases (Avants et al., 2008; Joshi et al., 2004; Reuter et al., 2012). These templates are typically built with MRI scans, since they are abundant, of approximately isotropic resolution, and provide excellent soft tissue contrast (Evans, 1992; Evans et al., 1993; Grabner et al., 2006; Mazziotta et al., 2001).

Most atlases include not only information on image intensities, but also some kind of semantic information in terms of voxel-wise labels. These labels are typically obtained via manual contouring by an expert, and can be made on the template directly or on the images that are used to build the template. The former has two advantages: *(i)* it requires $1/N$ times the manual delineation effort; and *(ii)* the increased signal-to-noise ratio of the template may make it easier to distinguish some regions of interest (ROI) that may not be clearly visible in the individual scans (e.g, nuclei of the amygdala, Tyszka and Pauli 2016). This atlases can be used in basic registration-based segmentation, where the template is spatially deformed to a target image with a nonlinear registration algorithm based on image intensities (Sotiras et al., 2013), and the labels are subsequently "propagated" to target space in order to automatically obtain a segmentation. This method was widespread in the earlier days of neuroimaging studies, when labelled data was very scarce (e.g., Collins et al. 1995; Dawant et al. 1999; Lancaster et al. 1997; Sandor and Leahy 1997).

While directly labelling a template remains popular when building atlases with high level of detail (and thus high manual delineation cost), the main downside is that the resulting atlas is not probabilistic. This is particularly problematic when describing brain areas where the anatomy is less consistent across subjects, particularly topological changes that cannot be modelled with a deformation. Seemingly, the resulting averaged intensities may create phantom boundaries on the template to be labelled, potentially inducing fictitious underlying anatomy. An alternative is to label the N individual images, which obviously requires much more delineation effort, but enables learning of the spatial distribution of the labels and their relationship with the underlying intensities. This approach also enables training of discriminative ML methods (best represented by deep convolutional networks), as described in Section 3 below.

Deriving atlases from N labelled scans can be done in a parametric or non-parametric fashion. Non-parametric atlasing approaches are best represented by the multi-atlas paradigm (Iglesias and Sabuncu, 2015), pioneered by Rohlfing et al. (2004), and applied to brain MRI by many others (e.g., Artaechevarria et al. 2009; Heckemann et al. 2006; Sabuncu et al. 2010; Wang et al. 2012). In its simplest form, this approach amounts to: registering a set of images with ground truth delineations (in this context knows as "atlases") to a target scan; propagating the delineations; and merging these warped label maps into a single estimate of the segmentation with a label fusion algorithm. This approach has the potential to better cover the spectrum of anatomical variability in a population than a single atlas. On the downside, it has higher computational cost associated with computing N nonlinear registrations – even though the running time of such algorithms has been greatly decreased by modern deep ML approaches (Fu et al., 2020; Haskins et al., 2020). Also, the resulting segmented volume may not preserve the topology of the atlases after label fusion (Xie et al., 2017).

Parametric approaches summarise the information of the N labelled cases into a "probabilistic atlas", endowed with statistical distributions over the labels and intensities. For example, the FreeSurfer atlas (Fischl et al., 2002) provides, at every voxel location, a vector of probabilities for the different classes, as well as a Gaussian distribution (mean and variance) for the image intensities conditioned on the class. Rather than modelling voxels individually, the atlas used for segmentation in FSL/FIRST uses Gaussian distributions to model the shape of brain structures (which are encoded as surfaces using point distribution models) and the image intensities along the surface normals (Patenaude et al., 2011).

A particular class of probabilistic atlases contain information exclusively on the neuroanatomical labels, i.e., they neglect the image intensities. Best represented by the atlas in SPM's Unified Segmentation (Ashburner and Friston, 2005), these atlases provide just a vector of probabilities for the different classes at every spatial location. These atlases are very popular in neuroimaging because, combined with an unsupervised likelihood model of image intensities (typically a Gaussian mixture model conditioned on the classes), they can analyse scans of *any* MR contrast. This is because the likelihood parameters (e.g., mean and variances) are estimated directly from the target scan (Ashburner and Friston, 2005; Van Leemput et al., 1999; Wells et al., 1996). These approaches also have the advantage that they enable the construction of atlases with *ex vivo* modalities, for subsequent application to the segmentation of *in vivo* scans with very different intensity profiles – which would be very difficult with discriminative methods due to the large domain gap. Our group has applied this technique to the construction of high resolution atlases of the hippocampus, amygdala and thalamus, using histology and *ex vivo* MRI (Iglesias et al., 2015; 2018; Saygin et al., 2017).

It is apparent from this section that the term "atlas" is highly ambiguous in neuroimaging. Throughout the rest of this article, we use "template" to refer to an average of co-registered images; "probabilistic atlas" to refer to a map of label probabilities; "template and associated probabilistic atlas" to refer to a combination of the two; and "multi-atlas" to refer to a set of images with associated segmentations.

2.2. Atlases built from MRI

Being the modality of choice for imaging the human brain *in vivo*, MRI is a common choice for building brain atlases of the subcortex. Here we review available atlases (summarised in Table 2) that describe one or multiple subcortical structures, classified by the modelled neuroanatomical region. Most of them are built from *in vivo* MRI, which avoids domain gaps with test data (as explained in Section 1 above), but some of them are also built at higher resolution with *ex vivo* MRI or histology.

2.2.1. MRI atlases of whole structures

Some atlases seek to describe large regions of the brain (if not the whole brain), and include a number of subcortical regions modelled at the whole structure level, i.e., without subdividing them into finer regions or nuclei. An example is the FreeSurfer atlas (Fischl et al., 2002), which is a probabilistic atlas built from $N = 40$ subjects and endowed with class-dependent Gaussian distributions for the intensities at each location. It includes subcortical regions such as TH, HP, AM, PU, PA, CAU, NA. The same training dataset has been used to build a probabilistic atlas of the same regions (i.e., without intensity information) for MR contrast-adaptive segmentation (Puonti et al., 2016). As explained in Section 2.1 above, the FSL/FIRST atlas (Patenaude et al., 2011) is also probabilistic, but rather than modelling voxels, it uses a point distribution model to describe the anatomical variation of several subcortical structures (TH, HP, AM, PU, PA, CAU, NA).

There are a number of atlases that provide a template and associated probabilistic atlas for a number of whole structures. For example, Keuken et al. (2014) built the "ATAG" atlas of the basal ganglia (PA, SN, STN, RN, ST) using 7T MRI to delineate these regions on multiparametric MRI (T1, T2*, QSM) from $N = 30$ subjects. In a similar manner, Wang et al. (2016) built a template and probabilistic atlas for the STN, SN, PA and RN using manual segmentations made on T1 and T2 MRIs of $N = 12$ cases acquired at high-resolution with a 7T scanner. Pauli et al. (2018) first combined T1 and T2 scans from $N = 168$ subjects from the Human Connectome Project (HCP) dataset (Van Essen et al., 2013) to build a template with high signal-to-noise ratio, and then segmented 16 subcortical grey matter regions (including CAU, PU, external and internal PA, STN, SN, HTh, RN, or VTA) on the template. The final segmentation is probabilistic as they averaged manual segmentations from three observers made on eight templates (built with different subsets of scans).

Some whole brain atlases are available both as probabilistic atlas and multi-atlas; the latter form is useful for researchers to run multi-atlas segmentation algorithms, build their own atlases, or train their own segmentation methods (more details in Section 3 below). One example is the widespread Mindboggle-101 dataset (Klein and Tourville, 2012)

Table 2
Summary of subcortical atlases derived from MRI, highlighting their type (multi-atlas, template, probabilistic), the number of available atlases, the MR contrasts available, strength and resolution, the number of labelled regions, and the targeted subcortical structures. We split the table with different subsections: whole-brain atlases, atlases targeting a single subcortical region (basal ganglia, thalamus and others) and atlases targeting multiple subcortical structures. Within each subsection, atlases are ordered by publication date. Asterisks (*) indicate that separate labels are available per hemisphere. N.A=not available; MTL=medial temporal lobe.

Atlas reference Templates	Atlas type	Num. atlases	MR contrasts	Field str.	Resolution (mm^3)	Num. classes	Subcortical structures
Evans (1992)	Template	250	N.A		N.A	-	-
Evans et al. (1993)	Template	305	T1w	1.5T	N.A	-	-
Mazziotta et al. (2001)	Template	~ 7000	T1w,T2w,PDw	N.A.	1x1x1	-	-
Grabner et al. (2006)	Template	153	T1	1.5T	0.86x0.86x2	-	-
			Whole-brain atlases				
Fischl et al. (2002)	Probabilistic	40	T1w	1.5T	1x1x1	36 (*)	TH, HP, AM, PU, PA, CAU, NA
Hammers et al. (2003)	Multiple / Probabilistic	20	T1w	1.5T	1x1x1	49 (*)	TH, HP, AM, PU, PA, NA, CAU
Shattuck et al. (2008)	Multiple / Probabilistic	40	T1w	1.5T	1x1x1	56 (*)	PU, CAU, HP
Patenaude et al. (2011)	Probabilistic	336	T1w	N.A.	1x1x1	15 (*)	TH, HP, AM, PU, PA, CAU, NA
Klein and Tourville (2012)	Multiple	101	T1w	Mult.	1x1x1	92	TH, HP, AM, PU, PA, CAU, NA
Keuken et al. (2014)	Probabilistic	30	T1w,T2*w, QSM	7T	1x1x1	6	PA (int/ext), STN, SN, RN, ST
Wu et al. (2016)	Multiple	90	T1w	3T	~1x1x1	286	TH, HP, AM, PU, PA, CAU, NA, HTh, SN, RN
Wang et al. (2016)	Probabilistic	12	T1w,T2w	7T	0.6x0.6x0.6	4	STN, PA, RN, SN
Puonti et al. (2016)	Probabilistic	39	T1w		1x1x1	38 (*)	TH, HP, AM, PU, PA, CAU, NA
Pauli et al. (2018)	Probabilistic	168	T1w,T2w	7T	0.7x0.7x0.7	16	CAU, PU, NA, AM, PA (ext/int), SN, STN, HTh, RN, VTA
Atlas reference	Atlas type	Num. atlases	MR contrasts	Field str.	Resolution (mm^3)	Num. classes	Subcortical structures
			Basal ganglia atlases				
Choi et al. (2012)	Template w/ labels	1000	fMRI	3T	0.5x0.5x0.5	5	ST (5)
Da Silva et al. (2017)	Template w/ labels	16	dMRI	3T	N.A.	5	PA (5)
Cartmell et al. (2019)	Probabilistic	245	dMRI (tract.)	3T	1.25x1.25x1.25	2	NA (2)
Alkemade et al. (2020)	Multiple/ Probabilistic	105	T1w, R1, R2*, T1, T2*, QSM	7T	0.64x0.64x0.7 / 0.5x0.5x0.5	19	STN, SN, RN, PA (ext/int)
			Thalamic atlases				
Behrens et al. (2003)	Probabilistic	8	dMRI (tract.)	1.5T	N.A	7	TH
Zhang et al. (2008)	Probabilistic	17	T1w,fMRI	3T	2x2x2	5	TH
Kumar et al. (2017)	Probabilistic	40	fMRI	N.A.	2x2x2	15	TH
Akram et al. (2018)	Probabilistic	9	dMRI (tract.)	3T	1x1x1	4	TH
Su et al. (2019)	Multiple	20	WM-nulled	7T	N.A	24 (*)	TH
Saranathan et al. (2021)	Multiple	9	WM-nulled	7T	0.7x0.7x0.5	24 (*)	TH
			Other single-structure atlases				
Yushkevich et al. (2009)	Template w/ labels	5	MRI	9.4T	0.3x0.2x0.2	5	HP
Accolla et al. (2014)	Probabilistic	13	dMRI	3T	1.7x1.7x1.7	3	STN
Kulaga-Yoskovitz et al. (2015)	Multiple	25	T1w,T2w	3T	1x1x1 / 0.4x0.4x2	3	HP
Iglesias et al. (2015)	Probabilistic	15	*ex vivo* T1w	7T	0.25x0.25x0.25	13	HP
Tyszka and Pauli (2016)	Template w/ labels	168	T1w,T2w	N.A.	0.7x0.7x0.7	9	AM
Saygin et al. (2017)	Probabilistic	10	*ex vivo* T1w	7T	0.25x0.25x0.25	9	AM
Zhang et al. (2017)	Probabilistic	485	dMRI,fMRI	3T	1.25x1.25x1.25 and 2x2x2	3	SN
Lau et al. (2020)	Template w/ labels	32	T1rlx	7T	0.5x0.5x0.5	11 (*)	ZI
			Other atlases with multiple structures				
Ahsan et al. (2007)	Multiple / Probabilistic	30	T1w	1.5T	1x1x1	12	TH, CAU, NA, PU, PA, SN
Entis et al. (2012)	Multiple	10	T1w	3T	0.38x0.8x0.38	4	AM (4)
Winterburn et al. (2013)	Multiple	5	T1w,T2w	3T	0.3x0.3x0.3	10 (*)	HP (5)
Berron et al. (2017)	Multiple	22	T2w	7T	0.44x1x0.44	10 (*)	HP and other MTL
Amaral et al. (2018)	Multiple	5	T1w,T2w	3T	0.3x0.3x0.3	16 (*)	HP (8)
Tullo et al. (2018)	Multiple	5	T1w,T2w	3T	0.3x0.3x0.3	6 (*)	ST, PA, TH
Tian et al. (2020)	Template	> 1000	fMRI	3/7T	2x2x2, 1.6x1.6x1.6	54 (*)	NA, TH, HP, AM, PA
Yu et al. (2021)	Template w/ labels	87	T1w,QSM,R2*, GREmag	3T	0.47x0.47x2	16 (*)	PU, CAU, ACC, PA, SN, RN, STN, TH (5)

available as a multi-atlas and used in many standard segmentation algorithms. Mindboggle-101 consists of a total of 101 subjects with manual delineations for a total of 92 structures, including both cortical and subcortical regions (TH, HP, AM, PU, PA, CAU, NA). Other examples are the LPBA40 atlas (Shattuck et al., 2008), the Adult IXI dataset (Hammers et al., 2003) or the MRICloud atlas (Wu et al., 2016). LPBA40 includes a template with an associated probabilistic atlas built from 40 subjects; it mostly models cortical regions, but also includes four subcortical structures (PU, CAU, HP, lateral ventricle). The MRI scans and manual delineations of the 40 subjects are available as a multi-atlas. The Adult IXI dataset comprises N=20 cases with segmentations for the TH, HP, AM, PU, PA, NA, CAU, among other regions, as well as a maximum probability template. And the MRICloud dataset contains a total of 90 subjects covering a large age span (4–82 years) targeting a total of 286 structures grouped in 5 hierarchical levels, among which many subcortical regions. Semi-automatic labels were computed by initially propagating single-atlas delineations (Oishi et al., 2009) to a subset of subjects which are then used in a multi-atlas setting to segment the remaining subjects. Each one of the segmentations (single-/multi-atlas) is manually corrected.

Finally, there is also a number of templates describing the intensities (but not labels) of the whole human brain, such as those already mentioned in Section 2.1 above (Evans, 1992; Evans et al., 1993; Grabner et al., 2006; Mazziotta et al., 2001), and which have become obsolete.

2.2.2. MRI atlases including subregions

Dedicated atlases focusing on the subregions of (typically) one or multiple structures have been proposed in the literature. In this section, we survey MRI atlases at the subregion level classified by anatomy.

Basal ganglia The basal ganglia has attracted a lot of attention, as it is a functionally rich area and a common target for DBS in diseases like Parkinson's. The most comprehensive MRI atlas of the basal ganglia is arguably the recently released AHEAD dataset (Alkemade et al., 2020), which includes manual delineations of 19 ROIs (including STN, SN, PA, and RN) made on high-resolution, multi-modal MRI of on $N = 105$ subjects (T1 weighted and quantitative R1-maps, R2*-maps, T1-maps, T2* maps, and QSM). AHEAD includes a multi-modal template with these channels, as well as an associated probabilistic atlas. Other works have focused on even more specific regions. Choi et al. (2012) used resting-state fMRI from $N = 1000$ subjects to subdivide the striatum into five cortical zones (linked to sensorimotor, premotor, limbic, and two association networks) using a topography globally consistent with monkey anatomical studies. They provide a probabilistic atlas in MNI space. Da Silva et al. (2017) used diffusion MRI from $N = 16$ subjects to subdivide the internal pallidum into five clusters based on their structural connectivity. They provide a (hard) average segmentation in MNI space. Cartmell et al. (2019) also used structural connectivity from $N = 245$ subjects to subdivide the accumbens into core and shell, and produced a probabilistic atlas in MNI space – which they validated with histology and CLARITY (Chung et al., 2013).

Thalamus The thalamus not only regulates a number of functions (consciousness, sleep and alert states; the motor system; or spoken language), but is connected via white matter pathways to virtually the entire cortex. For this reason, many atlases have been built to study its nuclei independently. Since the boundaries between most nuclei are indistinguishable in 1 mm structural MRI (e.g., T1- or T2-weighted *in vivo* scans), most parcellations are based on connectivity. In their seminal work, Behrens et al. (2003) used diffusion MRI data from $N = 8$ subjects to parcellate the thalamus into seven subregions based on their connectivity to different cortical areas, and produced a template with an associated probabilistic atlas. A number of other works have used similar approaches to produce templates with label probabilities. Zhang et al. (2008) used functional and structural connectivity from $N = 17$ subjects to subdivide the thalamus into motor/premotor, somatosensory, parietal/occipital, prefrontal and temporal functional zones. Akram et al. (2018) used probabilistic tractography from $N = 9$ subjects to locate the ventral intermediate nucleus and the dentato-rubro-thalamic tract – which are common targets in DBS for tremor. Kumar et al. (2017) used independent component analysis on resting state fMRI data from $N = 40$ subjects to subdivide the thalamus into 15 functionally distinct regions. Finally, there are a recent atlases of the thalamus that rely on structural MRI, rather than diffusion or fMRI: Su et al. (2019) and Saranathan et al. (2021) used white-matter-nulled imaging to enhance the contrast between the nuclei. Both works are multi-atlas comprising 12 thalamic nuclei delineated on $N = 20$ and $N = 12$ cases, respectively. The latter also provides maximum probability maps on MNI space.

Other single structures There are many other MRI atlases dedicated to structures other than the basal ganglia and the thalamus. For example, Accolla et al. (2014) used structural connectivity computed from diffusion MRI from $N = 13$ subjects to build a template and probabilistic atlas of the STN with three functional subregions: sensorimotor, associative, and limbic. In a similar fashion, Zhang et al. (2017) used spectral clustering on the diffusion and functional MRI data from $N = 485$ HCP subjects to create a probabilistic atlas of the substantia nigra in MNI space, with three functional subregions: limbic, cognitive, and motor. Yushkevich et al. (2009) built a high-resolution template of the hippocampus using *ex vivo* MRI from $N = 5$ cases, which they distribute along with an average segmentation of five subregions. In Iglesias et al. (2015), we also used high-resolution *ex vivo* MRI from $N = 15$ cases to build a probabilistic atlas of the hippocampus with 13 subregions. In follow-up work (Saygin et al., 2017), we followed a similar approach to extend the probabilistic atlas to the amygdala, with 9 nuclei delineated on $N = 10$ cases. Tyszka and Pauli (2016) also modelled the nuclei of the amygdala, by first creating a T1-T2 template with high signal-to-noise ratio from $N = 168$ HCP subjects, and then creating a (hard) manual segmentation on this volume. A similar approach as been recently used by Lau et al. (2020) to model the *zona incerta*: they created a high-contrast template by averaging T1 relaxometry at 7T from $N = 32$ subjects, and then used it to segment the caudal and rostral ZI, in addition to some surrounding structures. A multi-atlas approach for the hippocampus, the MNI-HiSub25 dataset, is presented in (Kulaga-Yoskovitz et al., 2015), where the hippocampus is divided into 3 identifiable regions on 3T *in vivo* MRI. MNI-HiSub25 is also available as a probabilistic atlas and has been used to train hippocampal segmentation algorithms (as explained in Section 3 below).

Multiple structures There are some atlases that cover multiple structures at the subregion level. One example is the CoBrALab atlas: in a series of papers (Amaral et al., 2018; Entis et al., 2012; Tullo et al., 2018; Winterburn et al., 2013), the Computational Brain Anatomy Lab (CoBrALab) from McGill University has described the labelling (manual or via registration) of 5 multimodal T1-w MRI scans at 0.3 mm isotropic resolution, in order to create a multi-atlas of the TH, PA, HP, AM, ST, and their subregions. Another example is the recently released Melbourne subcortex atlas (Tian et al., 2020), which covers the ST, TH, HP, AM, PA. This atlas is essentially a hierarchical parcellation of these structures using fMRI connectivity gradients derived from $N > 1,000$ subjects. The atlas consists of hard (maximum probability) parcellations at four different levels of granularity, in MNI space. As a last example, Berron et al. (2017) present an atlas focused on the medial temporal lobe, delineating not only several hippocampal nuclei but also surrounding cortical regions such as the entorhinal cortex, Brodmann areas 35 and 36 and the parahippocampal cortex. While previous atlases are built from healthy subjects, a disease-specific atlas for Parkinson's disease (PD) is presented in Yu et al. (2021). The atlas includes a total of $N = 87$ subjects diagnosed with PD targeting typical structures targeted in DBS as well as other neighbouring structures (PU, CAU, ACC, PA, SN, RN, STN, TH); moreover, they also provide a subdivision of the thalamus into 5 nuclei. The atlas has multiple templates available (T1w, quantitative susceptibility mapping, R2*, GRE magnitude and brain tissue probabilistic maps).

2.3. Atlases built from histology

Using dedicated stains and microscopic imaging, histology enables manual delineation – and thus atlas building – at a level of detail that is not possible with MRI, even *ex vivo*. The main disadvantage is the much larger effort that is required to acquire the data, as well as the substantial amount of spatial distortion introduced by blocking, processing, sectioning and mounting tissue. However, there is a whole literature on methods to recover the 3D structure of histological sections while correcting (or at least being robust against) artefacts like tissue folding and tearing (Pichat et al., 2018). In this section, we survey histological atlases classified by anatomy (summarised in Table 3).

2.3.1. Basal ganglia and thalamus

As for MRI, many histological atlases have been proposed for the basal ganglia and thalamus, due to their connection with DBS. One of the first histological atlases ever built was that by Chakravarty et al. (2006), who labelled over 100 subregions of the thalamus and basal ganglia on the 3D reconstructed histology of one case. This segmentation was transferred to a standard space (Colin27) using a synthetic MRI volume derived from the labels in the registration. The resulting template (Colin27) and (hard) labels can be used in registration-based segmentation. Chakravarty's atlas was recently upgraded by Ewert et al. (2018), who improved the segmentation using manual volumetric masks to guide it, and also added subdivisions of the STN and internal PA using a separate diffusion MRI dataset with 30 subjects. Xiao et al. (2017) also sought to improve Chakravarty's atlas, by adding regions such as the STN, which they manually traced on multispectral MR imaging (T1, T2*, R2* maps).

Other atlases have modelled the basal ganglia or thalamus independently. In an early work, Yelnik et al. (2007) used *ex vivo* MRI as reference to 3D reconstruct the histology of a single case, and labelled 80 ROIs of the basal ganglia on the registered sections. The resulting 3D segmentation and companion MRI could then be used for registration-based segmentation. In a similar fashion, Ilinsky et al. (2018) combined MRI and histology from $N = 4$ cases to build an atlas of the motor-related nuclei in the human thalamus in MNI space. Krauth et al. (2010) used 3D reconstructed histology from $N = 6$ cases to build a single average (hard) segmentation that represents the average thalamus. The same authors have subsequently deformed this segmentation into MNI space, so that it can be used in registration-based segmentation. He et al. (2020) recently combined Krauth's atlas with ATAG, and enhanced them with further subdivisions derived from fMRI from $N = 128$ subjects to produce a joint atlas of the basal ganglia and thalamus known as "ABGT". Finally, in Iglesias et al. (2018), we built a probabilistic atlas of 26 thalamic nuclei using 3D reconstructed histology from 6 cases (12 hemispheres).

2.3.2. Hippocampus

The hippocampus is of high interest due to its connections with memory, spatial navigation, and dementia like Alzheimer's disease, among others. While most existing hippocampal atlases have relied solely on MRI, Adler et al. (2018) combined histology with MRI to build an enhanced hippocampal atlas as follows. First, they built a template with $N = 31$ *ex vivo* MRI scans at 0.2 mm isotropic resolution, manually labelling the stratum radiatum lacunosum moleculare and the whole hippocampus. Then, they produced a hard subfield segmentation on the template space as the consensus of the deformed labels from 9 cases that were manually delineated based on the histology. Finally, they merge the subfield labels with the average MRI-based segmentation to yield the final probabilistic atlas. A similar approach is presented in Ravikumar et al. (2021), where they also include some surrounding cortical areas, such as the entorhinal and parahippocampal cortex and Brodmann areas 35 and 36.

[1] http://www.bic.mni.mcgill.ca/ServicesAtlases/ICBM152NLin2009.

Table 3
Summary of subcortical atlases derived from histology, highlighting the type (template, probabilistic), the histology sample size, the availability of paired MR contrasts, the use of external MRI contrasts to complement the histology sample, number of regions labelled, and targeted subcortical structures. The hypen ('-') indicates that doesn't apply.

Atlas Name	Atlas type	Histology sample	Paired MR	Extra MR contrasts	Num. labels	Subcortical structures
Chakravarty et al. (2006)	Template	1 specimen, 86 sections	–	–	123	TH, Basal Ganglia
Yelnik et al. (2007)	Template w/ labels	1 spec. 160 sect.	T1w,T2w	–	80	STN, SN, RN, ZI
Krauth et al. (2010)	Template w/ labels	6 spec.	–	–	42	TH, RN, STN
Xiao et al. (2017)	Template w/ labels	Chakravarty et al. (2006) atlas		N=25 (T1w, T2*w, T1-T2*, phase, R2*)	131	CAU, PU, PA, TH, STN, RN, SN
Ewert et al. (2018)	Template w/ labels	Chakravarty et al. (2006) atlas		ICBM152 template[1] (T1w, T2w, PD, T2rlx, dMRI)	92	PA, STN, RN, TH, SN, ZI
Adler et al. (2018)	Probabilistic	9 spec., 46 blocks, ~50 sect./block	*ex vivo* MR	N=31 (*ex vivo* MR)	6	HP subfields
Iglesias et al. (2018)	Probabilistic	6 spec.	*ex vivo* MR	N=39 (T1-w)	36	TH nuclei
Ilinsky et al. (2018)	Template w/ labels	1 spec.	*ex vivo* MR on blocks	–	47	ST, PA, TH, SN, STN, RN, HTh
He et al. (2020)	Template w/ labels	Krauth et al. (2010) atlas		N=96 (T1-w, fMRI)	21	ST PA, STN, SN, TH
Ravikumar et al. (2021)	Probabilistic	11 specimens	*ex vivo* MR	N=29 (*ex vivo* MR) Whole brain atlases	14	HP subfields + surrounding cortical
Amunts et al. (2013)	Template	1 spec. 7400 sections	*ex vivo* MR	–	None	Amunts et al. (2020), Wagstyl et al. (2020) DeKraker et al. (2020)
Ding et al. (2016)	Template w/ labels	1 spec. 106 sections	*ex vivo* MR	–	862	CAU, PU, AM, TH, PA, NA, HTh, SN, BF, HP, STN, ZI

Table 4
Summary of algorithms for subcortical segmentation. When multiple train/validation experiments are reported, only one is considered here because of space contratins. Algorithms with asterisks (*) include bilateral structures. "Main" subcortical structures comprise HP, PU, TH, CAU, PA, AM, NA. Dataset acronyms are: MALC (Multi-Atlas Labeling Challenge Data), and MNI-HiSub25 (Kulaga-Yoskovitz et al., 2015).

Method	Segmentation type	Training datasets	MR contrasts	Num. labels	Subcortical structures
		Whole-brain segmentation			
Fischl et al. (2002)	Bayes. seg.	Probabilistic atlas	T1w	36 (*)	Main
Heckemann et al. (2006)	Multi-atlas	*N*=30	T1w	66 (*)	Main
Khan et al. (2008)	Multi-atlas	Template	T1w	12 (*)	Main w/o AM
Rousseau et al. (2011)	Multi-atlas	*N*=18	T1w	32 (*)	Main
Patenaude et al. (2011)	Multi-atlas	*N*=336	T1w	15 (*)	Main
Asman and Landman (2013)	Multi-atlas	OASIS	T1w	25 (*)	Main w/o NA
Zikic et al. (2013)	Multi-atlas	MALC	T1w	134 (*)	Main
Wang et al. (2014)	Multi-atlas	MALC	T1w	28 (*)	Main
Puonti et al. (2016)	Bayes. seg.	Probabilistic atlas	Contr. adapt.	36 (*)	Main
Manjón and Coupé (2016)	Multi-atlas	N=100	T1w	14 (*)	Main
Kushibar et al. (2018)	2.5D CNN	MALC	T1w	14 (*)	Main
Wachinger et al. (2018)	3D CNN	MALC	T1w	25 (*)	Main
Roy et al. (2018)	2.5D CNN	MALC	T1w	27 (*)	Main
Dalca et al. (2019)	Bayes. seg.	Multi-dataset	T1w	36 (*)	Main
Li et al. (2019)	Multi-atlas	*N*=10	T1w, QSM	10 (*)	PA, TH, RN, SN, STN, PUT, CAU
Henschel et al. (2020)	2.5D CNN	Multi-dataset	T1w	95 (*)	Main
Coupé et al. (2020)	3D CNN	Multi-dataset	T1w	132 (*)	Main
Billot et al. (2021)	3D CNN	Multi-dataset	Contr. adapt.	30 (*)	Main
		Basal ganglia segmentation			
Haegelen et al. (2013)	Multi-atlas	*N*=57	T1w,T2w	14	STN, SN, RN
Xiao et al. (2014)	Multi-atlas	*N*=33	T1w,T2w	6 (*)	STN, SN, RN
Xiao et al. (2015)	Multi-atlas	*N*=10	4 contrasts	6 (*)	STN, SN, RN
Visser et al. (2016a)	Bayes. seg.	Template + Prob. atlas	Multimodal	4 (*)	ST, PA
Visser et al. (2016b)	Bayes. seg.	Template + Prob. atlas	T2w, QSM	6 (*)	STN, SN, RN
Choi and Jin (2016)	3D CNN	MALC	T1-w	1	STR
Milletari et al. (2017)	3D CNN	*N*=55	T1w	26 (*)	Multiple.
Kim et al. (2019)	Discriminative	*N*=46	T2w	2	STN, SN
Park et al. (2019)	3D CNN	*N*=102	T2*	4 (*)	STN, RN
Baxter et al. (2020)	3D CNN	*N*=9	T1w,T2w	2(*)	STN
Solomon et al. (2021)	3D CNN	*N*=58	T2w	2	PA
		Thalamic segmentation			
Behrens et al. (2003)	Prob. tracto.	-	T1w, DWI	4/6	TH nuclei
Johansen-Berg et al. (2005)	Prob. tracto.	-	T1w, DWI	7	TH nuclei
Stough et al. (2014)	Discriminative	N=12	T1w, DWI	12 (*)	TH nuclei
Akram et al. (2018)	Prob. tracto.	-	T1w, DWI	4	TH nuclei
Jaimes et al. (2018)	Prob. tracto.	-	T1w, DWI	4–7	TH nuclei
Middlebrooks et al. (2018)	Prob. tracto.	-	T1w, DWI	6	TH nuclei
Iglesias et al. (2018)	Bayes. seg.	Probabilistic atlas	Contr. adapt.	26 (*)	TH nuclei
Su et al. (2019)	Multi-atlas	N=20	WM-nulled	12	TH nuclei
Datta et al. (2021)	Multi-atlas	N=20	T1-MP2RAGE	12	TH nuclei
		Hippocampal segmentation			
Van Leemput et al. (2009)	Bayes. seg.	N=10	T1-w	7	HP nuclei
Yushkevich et al. (2010)	Multi-atlas	N=32	T1w,T2w	7	HP nuclei
Pipitone et al. (2014)	Multi-atlas	N=3	T1-w	6	HP nuclei
Yushkevich et al. (2015b)	Multi-atlas	N=32	T1w,T2w	9	HP nuclei
Iglesias et al. (2015)	Bayes. seg.	Probabilistic atlas	T1-w	13	HP nuclei
Wisse et al. (2016)	Multi-atlas	N=30	T1w,T2w	6	HP nuclei
Caldairou et al. (2016)	Multi-atlas	MNI-HiSub25	T1w,T2w	3	HP nuclei
Yang et al. (2020)	3D CNN	MNI-HiSub25	T1w,T2w	3	HP nuclei
Goubran et al. (2020)	3D CNN	Multi-dataset	T1w	1	HP
		Segmentation of other structures			
Saygin et al. (2011)	Tractography	N=36	DWI	4	AM nuclei
Chakravarty et al. (2013)	Multi-atlas	N=1/20	T1-w	3	STR, PA, TH
Saygin et al. (2017)	Bayes. seg.	Probabilistic atlas	T1-w	9	AM nuclei
Billot et al. (2020)	3D CNN	N=37	T1-w	5 (*)	HTh nuclei
Bazin et al. (2020)	Bayes. seg.	N=105	Multi-modal	31 (*)	Multiple
Greve et al. (2021)	3D CNN	N=39	clinical T1-w	6 (*)	Limbic regions

2.3.3. *Whole brain*

Finally, there have been two noteworthy projects seeking to build atlases of the whole brain using histology. The first one is BigBrain (Amunts et al., 2013), which comprises densely cut sections of a single whole brain (over 7000 sections), 3D reconstructed with very high accuracy with the help of a reference *ex vivo* MRI. Despite the fact that BigBrain does not contain any manual delineations, there have been recent efforts to produce such labels for a number of structures (e.g., Amunts et al. 2020; DeKraker et al. 2020; Wagstyl et al. 2020).

The second project is the Allen human brain atlas (Ding et al., 2016), which consists of serial histology of a single hemisphere. Even though it does not comprise as many histological sections as BigBrain, it has the advantage of containing manual delineations for 862 ROIs on 106 select sections. The histology in the Allen atlas is not 3D reconstructed, which

precludes use in 3D analysis, but there have been efforts to remove its spatial distortions (Casamitjana et al., 2021; Mancini et al., 2020).

3. *In-vivo* segmentation of subcortical structures

Identifying neuroanatomical ROIs *in-vivo* from MRI (Eickhoff et al., 2018) via image segmentation enables an array of analyses in neuroimaging studies, including morphometry, connectivity (structural and functional), or planning of surgery and placement of DBS devices. Initially, manual delineation of brain ROIs was used as a robust and accurate solution to study a single or few cases. Nonetheless, manually tracing 3D volumes is time consuming and poorly reproducible. Hence, many automatic segmentation methods have been developed throughout the last three decades to circumvent these limitations. Such algorithms need to be reproducible, robust to acquisition parameters, and generalisable to anatomical differences. Bayesian and multi-atlas segmentation dominated the field in its early days; more recently, ML methods have superseded Bayesian algorithms and have created new opportunities in research due to their higher accuracy and faster inference times.

In this section, we first review the different types brain MRI segmentation methods based on atlases and ML. Then, we survey existing methods for the segmentation of different subcortical regions. Most of the mentioned algorithms rely on atlases (single-, multi- or probabilistic) introduced in the previous section, each of which use different protocols for ROI delineation, e.g., with varying anatomical definitions or levels of granularity. For example, Yushkevich et al. (2015a) found considerable differences between hippocampal segmentation protocols in a study with 21 sites. There are ongoing efforts seeking to reduce this variability, e.g., the work of the hippocampal subfield group (Olsen et al., 2019; Wisse et al., 2017b) and the organisation of subcortical segmentation challenges Landman and Warfield (2012)). Other works attempt to reconcile the mismatch between segmentation methods by comparing them analytically (Alexander-Bloch et al., 2018; Bohland et al., 2009; Yaakub et al., 2020).

3.1. Types of segmentation methods

Two main types of approaches have dominated the field of *in vivo* brain MRI segmentation: atlas-based approaches, and discriminative voxel classifiers – initially based on classical ML approaches, and more recently on deep neural networks.

3.1.1. Atlas-based segmentation

Atlas-based methods have capitalised on the success of image registration techniques in brain MRI (Sotiras et al., 2013), combined with the atlases surveyed in Section 2 above. Registration can be used to obtain a deformation field that warps an atlas to a target image to segment; this field can then be used to propagate the atlas label information accordingly.

As explained in the Section 2.1, the way in which the final segmentation is computed in target space depends on the type of atlas. In the case of a single labelled template, one typically propagates the available labels or label probabilities directly (Collins et al., 1995; Lancaster et al., 1997). If multiple labelled templates are available (i.e., multi-atlas segmentation), different label fusion methods can be used to merge the deformed atlas labels into a single estimate of the (possibly probabilistic) segmentation. Early label fusion relied on vanilla majority voting (Rohlfing et al., 2004), and has been superseded by techniques that give higher weight to more accurately registered atlases using, for instance: image similarity, measured with local cross-correlation (Artaechevarria et al., 2009) or Gaussian kernels (Sabuncu et al., 2010); regression techniques (Wang et al., 2012); patch-based feature matching (Rousseau et al., 2011); or, more recently, deep ML approaches (Xie et al., 2021).

In the case of probabilistic atlases, the propagation of label information is often posed as a Bayesian inference problem within a generative model of MRI scans. Essentially, segmentation seeks to answer the question: "given the prior distribution of segmentations (and possibly image intensities) encoded in the atlas, and given the observed MR intensities of a scan, what is the most likely segmentation according to the generative model?" In this framework, the atlas registration can be precomputed (Van Leemput et al., 1999) or estimated simultaneously with the segmentation in an unified framework (Ashburner and Friston, 2005; Pohl et al., 2006; Puonti et al., 2016). Crucially, the model of image intensities can be supervised or unsupervised. The former is potentially more robust, but limits the application of the method to images of the same contrast as the atlas (Fischl et al., 2002). The latter, on the other hand, adapts to the MR contrast of the target scan, most often by fitting a Gaussian mixture model to the distribution of image intensities, conditioned on the segmentation (Ashburner and Friston, 2005; Puonti et al., 2016; Van Leemput et al., 1999; Wells et al., 1996; Zhang et al., 2001). This *contrast-adaptive* ability makes this approach very robust to variations in MR contrast, which is very desirable when methods are made publicly available.

Finally, there are some atlas-based segmentation methods that rely on models of intensity profiles for whole regions, similar to active shape and appearance models (Cootes et al., 2001; 1995). As in the previous case, Bayesian inference can be used to find a segmentation that complies with the model both in terms of shape and appearance. Examples include the "m-reps" framework (Pizer et al., 2003) and the widespread FSL/FIRST tool (Patenaude et al., 2011) – in which compliance with the shape model ensures smooth, plausible segmentations.

3.1.2. Discriminative voxel classifiers

Discriminative models learn a direct mapping between input features and target variables. They are often applied to image segmentation by casting the task as a voxel classification problem, i.e., learning to predict labels from image intensities directly. Learning happens most often in a supervised fashion, i.e., from a set of images with ground-truth segmentations, typically obtained via manual delineation.

Early works only considered the intensities of the voxel at hand (possibly multispectral, e.g., T1-T2) directly as features (i.e., no neighbourhood information), and used simple classifiers such Gaussian classifiers or shallow neural networks to predict the segmentation (Clarke et al., 1993; DeCarli et al., 1992). Voxel-wise methods are very limited due to the overlaps of the intensity distribution of many brain structures, and can only be use to segment coarse tissue classes (grey matter, white matter, and cerebrospinal fluid).

Subsequent approaches in the two-thousands relied on sets of handcrafted features that described the neighbourhood of each voxel. Features used in the literature include: Gaussian scale space derivatives (Van der Lijn et al., 2011), Haar wavelets (Tu et al., 2008), shape probabilistic priors (Powell et al., 2008) or spatial coordinates (Morra et al., 2008), among others. The overall number of features can be very large in some cases, e.g., 18,000 in Morra et al. (2008). These features are fed to a classifier. Earlier works relied on k-nearest neighbours (Warfield et al., 2000) and support vector machines (Golland et al., 2005). Boosting strategies based on ensembles that reduce bias and variance (Breiman, 1996) gained popularity in the second half of the two-thousands. For example, Morra et al. (2009) used AdaBoost (Freund and Schapire, 1997) to segment the hippocampus, and Tu et al. (2008) used Probabilistic Boosting Trees (Tu, 2005) to segment four subcortical structures. In the first half of the 2010s, decision forests (Breiman, 2001; Criminisi et al., 2012) – which are an ensemble of decision trees – became the prevalent classifier in brain image segmentation, due to their increased accuracy (e.g., Pereira et al. 2016; Zikic et al. 2013).

The modern literature on brain MRI segmentation is dominated by deep convolutional neural networks (CNN), which simultaneously perform feature extraction (by optimising convolutional kernels) and classification (LeCun et al., 1998). Due to sequential processing through

nonlinearities, CNN are capable of modelling highly complex functions (Cybenko, 1989), and their ability to automatically learn features in a data-driven and task-oriented fashion endows them with unsurpassed accuracy. CNNs are typically trained on graphics processing unit (GPUs), in an iterative procedure that is much slower than its classical counterparts (e.g., SVMs or random forests). However, once trained, they are computationally very efficient, and can often process new cases in a few seconds. Segmentation CNNs are best represented by the U-net architecture Ronneberger et al. (2015), which includes a contractive and an expansive path in order to exploit features computed at different resolution levels.

Segmentation CNNs can be trained in 2D or 3D. The former has two major advantages: it alleviates the GPU memory requirements that are required in 3D setups, and it enables direct use of methods developed by the computer vision community (which generally works with 2D natural images). However, it also has the disadvantage that 3D context is ignored in segmentation. This problem can be alleviated in two manners: complementing image intensities with spatial features, such as atlas probabilities (Kushibar et al., 2018) or voxel coordinates (Wachinger et al., 2018); and using so-called 2.5D approaches, where three separate CNNs are trained in orthogonal orientations (sagittal, axial, coronal) and the results aggregated (Henschel et al., 2020; Kushibar et al., 2018; Roy et al., 2018).

Compared with Bayesian-based approaches on atlases, the main disadvantage of voxel classifiers (including CNNs) is the limited ability to generalise to MR contrasts other than that of the training data, due to the domain gap between the intensity distributions of the images at training and testing. Such distributional shifts can be mitigated with augmentation (Shorten and Khoshgoftaar, 2019) and domain adaptation techniques (Wang and Deng, 2018) when they are small, but remain problematic across different MRI contrasts.

3.2. Whole-brain segmentation

Whole-brain segmentation methods typically involve tens of lateralised brain structures, often including several subcortical structures. Some of the most popular protocols used in the reported methods are the CMA[2] protocol from the Center for Morphometric Analysis in the Massachusetts General Hospital, the BrainCOLOR[3] protocol provided by Neuromorphometrics, and extensions thereof (all derived from *in vivo* MRI). One of the first attempts to whole brain segmentation was Fischl et al. (2002), which presents a Bayesian inference framework that models MRI with a probabilistic atlas of neuroanatomy and intensities, combined with a Markov random field. The label posterior probabilities are then computed using iterated conditional modes (Besag, 1986). The method is publicly available in Freesurfer (Fischl, 2012), and segments 36 structures, including left and right HP, AM, TH, PA, PU, CAU, NA. This method cannot handle MR contrasts that do not coincide with that of the training data (1 *mm* T1 scans, in the FreeSurfer case). A contrast-adaptive alternative based on a probabilistic atlas and unsupervised intensity modelling ("SAMSEG") was presented by Puonti et al. (2016). SAMSEG is also available as part of FreeSurfer, segments the same 36 structures, and is resilient to changes in MR contrast, pulse sequence and scanning platform. Both methods use the CMA protocol.

Another widespread whole-brain segmentation method is FIRST (Patenaude et al., 2011), which is implemented in FSL (Jenkinson et al., 2012) and based on the FSL/FIRST probabilistic atlas previously presented. FIRST builds on the principles of active shape models (Cootes et al., 1995) and active appearance models (Cootes et al., 2001) within a Bayesian framework and provides smooth, anatomically plausible segmentations. FIRST segments 15 brain structures following the CMA guidelines, including left and right HP, AM, TH, PA, PU, CAU, NA.

[2] https://freesurfer.net/fswiki/CMA.

[3] https://mindboggle.info/braincolor/.

Many whole brain segmentation methods are based on image registration. Khan et al. (2008) use FreeSurfer to initialise a template with labels, which is used together with large deformation diffeomorphic mapping (LDDM, Beg et al. (2005)) to propagate the structures of interest (HP, PU, TH, CAU, PA, NA) to the target scan. LDDM is also used in Li et al. (2019), a multi-atlas approach that use a multi-modal input (T1w, QSM) to better segment structures from the basal ganglia. Heckemann et al. (2006) use multi-atlas segmentation with 30 atlases from young adults with expert segmentations for 66 brain structures, including HP, PU, TH, CAU, PA, AM, and NA according the widespread protocol defined by Hammers et al. (2003) using *in vivo* MRI.

Other multi-atlas methods for whole brain segmentation have been proposed in the literature. Asman and Landman (2013) use a non-local correspondence metric to measure similarity between atlases and target image. Wang et al. (2014) select the most relevant atlases for every voxel and use majority voting only on the most similar atlases. Both methods use $N = 15$ atlases from the MICCAI 2012 Multi-Atlas Labelling Challenge (MALC, Landman and Warfield (2012)) and segment the HP, PU, TH, CAU, PA, AM following the BrainCOLOR protocol. A pairwise and a global weighted average strategy using a non-local means filter was used by Rousseau et al. (2011) to segment the brain into 32 structures, among which the HP, PU, TH, CAU, PA, AM, NA as defined by the CMA protocol. Finally, a patch-based label fusion is used in volBrain Manjón and Coupé (2016), an online tool that segments main subcortical structures (HP, PU, TH, CAU, PA, AM, NA) on T1w images from a template library of size $N = 100$. The authors do not report the protocol used.

Deep CNNs for whole brain segmentation are typically trained on 1 mm T1 scans, which is the most frequent acquisition in neuroimaging research (for neuromorphometry purposes). Usually, CNN based methods are evaluated on multiple datasets and thus, different heterogeneous protocols Roy et al. (2018) seek to exploit large amounts of existing unlabelled scans by first pretraining a CNN with segmentations automatically obtained from those scans using FreeSurfer, and then finetuning on a small subset of manually labelled scans. They segment a total of 27 structures, including HP, AM, TH, PA, PU, CAU, NA. FastSurfer (Henschel et al., 2020) also relies partly on automated segmentations obtained with FreeSurfer, and yields labels for 95 lateralised cortical and subcortical structures, including HP, AM, TH, PA, PU, CAU, NA. On the same line, AssemblyNet (Coupé et al., 2020) uses the teacher-student framework to leverage knowledge from a subset of unlabelled images. It combines atlas priors with a large ensemble of CNNs to segment a total of 132 structures, including bilateral HP, AM, NA, CAU, PA, PU and TH.

Recently, our group has proposed two types of segmentation CNNs that can segment MR scans of any contrast. In Dalca et al. (2019), we use a CNN to predict the model parameters (means, variances, atlas deformation) of a Bayesian segmentation method with unsupervised likelihood. This CNN can be trained in an unsupervised fashion to segment scans of a pre-specified MR contrast, using the same objective function that is optimised in Bayesian segmentation. In Billot et al. (2021), we use a generative model inspired by that of Bayesian segmentation to generate images of random, unrealistic contrast at every mini-batch, and use them to train a U-net in a supervised fashion. The resulting CNN ("SynthSeg", also available in FreeSurfer) can then segment scans of any MR contrast without retraining. Both approaches are trained with the same datasets as FreeSurfer and SAMSEG, and thus segment the same set of subcortical structures (HP, AM, TH, PA, PU, CAU, NA).

3.3. Segmentation of specific subcortical structures

Due to their large number, small size, and low contrast, only a subset of existing subcortical nuclei have been historically included in whole brain segmentation algorithms (7% according to Forstmann et al. 2017). One of the attempts to cover a larger number of subcortical nuclei is presented by Bazin et al. (2020), who include 14 subcortical structures (ST, TH, AM, PA (ext/int), SN, STN, RN, CL, VTA, Fx, PAG, PPN and IC) in a Bayesian segmentation approach built with the AHEAD

dataset (Alkemade et al., 2020). However, most existing algorithms are restricted to a single structure of interest or a pre-defined portion of the input scan, typically a cuboid. This allows researchers to focus on a lower number of nuclei, which reduces the complexity of the problem and facilitates the manual delineation of the images.

3.3.1. Basal ganglia

Segmentation of ROIs of the basal ganglia *in-vivo* is useful in many applications, e.g., DBS, where accurate segmentation is critical to improve treatment efficacy and reduce adverse effects. Widespread targets include the PA, specially its internal segment, and the STN (Mao et al., 2019). Both the PA and the STN, as well as most basal ganglia nuclei, exhibit better T2 contrast than T1. Since the latter is preferred to inform the segmentation of surrounding structures or in multi-atlas registration, multimodal approaches are often used to segment basal ganglia ROIs. For example, the works by Xiao et al. (2015, 2014) use T1-w and T2-w contrasts in multi-atlas segmentation of the STN, SN and RN. To reduce manual labelling effort, the work from Visser et al. (2016a) uses a single reference atlas and several unlabelled training datasets with multiple contrasts in a Bayesian segmentation approach (MIST) to segment STR and PA. In their follow-up work, Visser et al. (2016b) use an enhanced version of MIST to segment smaller-sized nuclei, such as STN, SN and RN, using T1-w, T2*-w and QSM contrasts. Patch-based label fusion has also been applied to the basal ganglia, e.g., by Haegelen et al. (2013), who segment the STN, SN and RN, as well as some neighbouring structures (AM, HP, PU, TH).

Several CNN-based algorithms have been applied to basal ganglia segmentation in the last few years. Most of them are restricted to a single or just a few ROIs: Choi and Jin (2016) segment the STR from T1-w images; Park et al. (2019) segment the STN and RN from T2w images; Baxter et al. (2020) employ a multi-resolution CNN to detect and segment the STN from multimodal T1w/T2w inputs; and Solomon et al. (2021) segments the PA into internal and external segments using 7T T2w scans. Milletari et al. (2017) present a CNN that segments several basal ganglia nuclei (PA external/internal, SN reticula/compacta, RN, NA) as well as some surrounding structures (e.g., HP, AM) in clinical T1-w scans.

The protocols used in basal ganglia segmentation methods are typically informed by the Atlas of the Human Brain (Mai et al., 2015) and the Duvernoy atlas (Naidich et al., 2009).

3.3.2. Thalamus

Since the lateral and internal boundaries of the thalamus are not always clearly visible in standard T1/T2 images, many *in vivo* studies targeting this structure are based on diffusion MRI – which, despite its lower resolution, provides better contrast. Segmentation methods for diffusion MRI have relied on probabilistic tractography or clustering techniques. The pioneering work from Behrens et al. (2003) parcellates the thalamus based on their structural connectivity to cortical regions, and was followed up by many others, e.g., (Akram et al., 2018; Jaimes et al., 2018; Johansen-Berg et al., 2005; Middlebrooks et al., 2018). The main cortical targets slightly differ between works and include the motor cortex with different level of granularity (primary motor cortex, supplementary motor area, premotor cortex), the primary somatosensory zone and the occipital, temporal and parietal areas. An alternative to diffusion MRI is to use dedicated (non-diffusion) MRI pulse sequences to generate image contrast that enables thalamic segmentation. For example, the THOMAS framework, presented in Su et al. (2019), uses a white-matter-nulled (WMn) sequence to segment the thalamus into 12 different nuclei using a multi-atlas approach. Or Datta et al. (2021) investigate the use of a MP2RAGE sequence to synthesise WMn images and use the THOMAS framework. The details of the protocol used in both works can be found in Tourdias et al. (2014). Yet another alternative is to use multimodal imaging features to generate the required contrast. For example, Stough et al. (2014) fed intensity, connectivity and diffusivity-based features into a random forest classifier to parcellate the thalamus into six different groups of nuclei.

Finally, some approaches have relied on histological atlases (presented in Section 2.3 above) for localisation of smaller nuclei. For example, Chakravarty et al. (2013) use a single histological atlas Chakravarty et al. (2006) and multiple templates to segment the thalamus as well as some basal ganglia structures (STR, PA). Our group also used a histological atlas to segment 26 bilateral thalamic nuclei from MR images of arbitrary contrast with a Bayesian algorithm (Iglesias et al., 2018).

3.3.3. Hippocampus

Due to its connection with memory and diseases like Alzheimer's (Vemuri and Jack, 2010) or hippocampal sclerosis (Malmgren and Thom, 2012), the segmentation of the hippocampal substructures from *in vivo* MRI has attracted a lot of interest. The most targeted ROIs in the literature are the subiculum, cornus ammonis CA 1–3, and dentate gyrus (Yushkevich et al., 2015a). A wide variety of hippocampal segmentation protocols have been proposed in the literature (Yushkevich et al., 2015a), with main differences on the number of targeted subregions and the covered extension along the major axis of the hippocampal formation.

In standard research MRI scans at 1 mm isotropic resolution, the boundaries of the nuclei are generally not visible, hindering the training and validation of both manual and automatic segmentation methods. High resolution atlases are typically used to overcome this limitation, built from, e.g., *ex vivo* MRI at high field. An example is our probabilistic atlas (Iglesias et al., 2015) built from 15 *ex vivo* 7T FLASH images at 0.10-0.15 *mm* isotropic resolution, which is available in FreeSurfer, and can be used to segment the hippocampal subfields from scans of any MRI contrast. This method is mainly based on the hippocampal characterization of Rosene and Hoesen (1987).

In vivo study of hippocampal subregions often uses a dedicated T2w sequence at 0.4x2x0.4 mm^3 resolution centred at the hippocampal formation. For example, the ASHS algorithm (Yushkevich et al., 2015b) and its precursor (Yushkevich et al., 2010) use this sequence in a multi-atlas segmentation approach. Their follow-up work (Wisse et al., 2016) adapted ASHS to 7T MRI images. This type of sequence has been also been exploited by CNN segmentation methods (Yang et al., 2020). The ASHS segmentation protocol is derived from the work in Mueller and Weiner (2009) and has been extended throughout the years. T1-weighted contrast has also been used for hippocampal subregion segmentation, particularly at high resolution, e.g., by Van Leemput et al. (2009), who applied a Bayesian segmentation method to 0.38x0.8x0.38 mm^3 *in vivo* scans. Pipitone et al. (2014) used a publicly available 0.3 *mm* isotropic dataset (Winterburn et al., 2013) to segment scans acquired at standard resolution (1 *mm* isotropic) using a multi-atlas approach. A 3D CNN is trained to segment the whole hippocampus in subjects with extensive atrophy in Goubran et al. (2020). Finally, surface-based methods (DeKraker et al., 2021) are also used to segment the hippocampus; for example, Caldairou et al. (2016) used the MNI-HiSub25 atlas introduced in Section 2 in a multi-atlas setting combining surface-based processing and a patch-based template library.

3.3.4. Other subcortical structures

Other regions have been also targeted in *in-vivo* segmentation algorithms. One example is the amygdala. Saygin et al. (2011) used probabilistic tractography to segment its substructures. We extended our hippocampal atlas based on *ex vivo* MRI to model nine amygdaloid nuclei (Saygin et al., 2017). More recently, different CNN-based approaches have been proposed to segment regions from limbic system. For example, the hypothalamus has been targeted as a whole in Rodrigues et al. (2020), and segmented into 5 nuclei by our group in Billot et al. (2020). Our group has also published a CNN that segment several limbic structures (SepN, NA, BF, mamillary bodies and the anterior commissure; see Greve et al. 2021).

4. Open challenges and opportunities created by ML

Machine learning is a powerful technique for brain segmentation, as it is able to model complex relationships between appearance and the underlying anatomy in *in vivo* MRI. In addition, CNN-based methods perform fast inference on target scans, which makes them suitable for large scale processing of medical imaging datasets. Nonetheless, ML carries several associated challenges in terms of computational constraints, modelling, robustness and validation. Addressing these challenges will help towards the standardisation of these methodological approaches for widespread use within the community, to continue increasing our understanding the brain – including uncharted subcortical regions.

4.1. Computational requirements

Detailed modelling of the subcortex requires imaging at high resolution and segmentation with a large number of different labels. These requirements pose a challenge for training ML models: the CNNs typically used for segmentation are trained with GPUs that are much faster than their CPU counterparts, but are also more limited in terms of memory. For example: if we were to naively train a CNN to segment 200 labels using cubic patches with 100 mm width at 0.25 mm resolution, the last layer alone would require 50GB of memory, which is more than what high-end GPUs have available.

There exists several ways to alleviate GPU memory requirements during training. Patch-based training with smaller cuboids appears as a natural solution, but the lack of spatial context may lead to inconsistent predictions. Instead, 3D multi-scale methods combine fine-grained features extracted using patch-based methods with contextual features encoding the position of each patch in the 3D space (Kamnitsas et al., 2017). This is often implemented as two feature extractors (or encoders) at different resolutions, merged and fed into a single classifier (or decoder).

Another memory saving alternative is to use 2.5D modelling (Henschel et al., 2020; Roy et al., 2018), which circumvents the cubic growth in memory requirements with patch size. These approaches perform label fusion on 2D predictions from each orthogonal plane (axial, coronal, sagittal). This way, they can use full-resolution slices while benefiting from complementary information from orthogonal planes, and thus being able to correct (to some extent) spuriously mislabelled voxels. The lack of volumetric context with respect to 3D approaches is often mitigated by including some neighbouring slices as channels in the input layer.

4.2. Robustness

High-resolution scenarios with many labels also exacerbate some well-known performance issues of CNN-based segmentation, compromising their robustness. One such challenge is the unbalanced structure of the segmentation problem, where larger ROIs (e.g. cortical GM) coexist with small subcortical nuclei (e.g., alveus). Loss functions need to be carefully designed to handle this unbalance.

Another challenge is the lack of guarantee that CNNs will yield plausible segmentations – compared with, e.g., atlas-based methods. Current CNNs rarely used explicit anatomical constraints during training or training. One option is to include shape priors as input of the model in the form, e.g., of probabilistic atlases, to restrict the search space (Dalca et al., 2019; Kushibar et al., 2018). Another option is to filter the prediction to make it look more plausible by using, e.g., denoising autoencoders (Larrazabal et al., 2020).

Finally, robustness of CNNs is also compromised by the domain gap. Generalisable CNNs need to cope with wide variations in acquisition (MR contrast, resolution), artefacts, orientation, and anatomy. However, CNNs are relatively fragile, compared with, e.g., Bayesian methods. Nevertheless, we believe that the increasing availability of publicly available, large-scale, multi-modal, heterogeneous datasets will help the community develop methods with increased robustness. In addition, advances in data augmentation (such as our recent work on domain randomisation, Billot et al. 2021) also promise to deliver more robust methods.

4.3. Validation

Another outstanding challenge is the validation of *in vivo* brain MRI segmentation with high-resolution atlases – particularly those derived from histology. The conventional gold standard in segmentation is manual delineation by an expert, which enables the computation of direct validation metrics such as Dice scores and surface distances. However, the small substructures that are often present in histological atlases are seldom amenable to manual tracing on *in vivo* scans; this is the reason why atlases including such structures are built with histology in first place.

The are several possible strategies to ameliorate this problem. The ideal solution would be to compile datasets with paired, well registered histology and *in vivo* (or at least cadaveric) MRI (e.g., Goubran et al., 2016; Wisse et al., 2017a). This would enable direct propagation of high resolution labels to the MRI scan. However, this approach is problematic due to three factors. First, the logistical problems associated with either the need for identifying cases with an MRI close to death, or with cadaveric imaging (e.g., “cold brain effects”, Tofts et al. 2008). Second, the intrinsic difficulty of registering histology and MRI (Pichat et al., 2018), which deteriorates the quality of the ground truth labels. And third, the limited sample sizes due to the huge amount of work that is required for each case (histology, scanning, delineation).

Another alternative is the use of *ex vivo* MRI, which enables the manual delineation of many more ROIs than its *in vivo* counterpart, and can be downsampled to simulate *in vivo* resolutions. However, this approach has three disadvantages. First, *ex vivo* scanning requires specific expertise (and ideally dedicated hardware, e.g., coils) that are not present at every research centre. Second, the difference in MR contrast between *in vivo* and *ex vivo* MRI makes it difficult to draw conclusions on the former, based on results on the latter. And third, the large amount of required manual labelling also limits sample sizes.

A third alternative enabling direct evaluation is manual delineation on *in vivo* MRI of *groups* of nuclei that are visible in the scans, e.g., groups of thalamic nuclei (Glaister et al., 2016). This approach does not suffer from misregistration issues and enables larger sample sizes, but also has the disadvantage of not evaluating segmentation at the most granular level: how well do the subregions in a group fit the images, when their segmentation is driven by the external boundary of the group?

Rather than using direct evaluation techniques, one can also resort to indirect evaluation: instead of comparing segmentations against a gold standard, one evaluates them via their usefulness in downstream tasks, e.g., the ability to discriminate two groups between which differences are expected to exist. While this type of criterion is only a proxy for segmentation quality, it has the advantage of not requiring any manual tracing, thus enabling large sample sizes.

While the choice of validation method is often related to the availability of data, manpower, and anatomical expertise, we believe that it should ultimately be linked to the final application. For example, indirect evaluation in DBS should be directly related to the probability that the right ROI is stimulated, while in volumetric neuroimaging studies, correlation with the ground truth volume is likely to be a better proxy.

5. Conclusion

In this article, we have reviewed the two main pillars of human subcortex imaging: atlasing and segmentation. We have surveyed atlases derived from *in vivo* MRI, which are more easily applicable to other *in vivo* MRI scans, and atlases derived from *ex vivo* modalities (histology, *ex vivo* MRI), which enable description of the subcortex at a higher level

of detail. We have also surveyed methods for automatically segmenting subcortical structures from *in vivo* brain MRI scans – from earlier registration-based methods to recent ML approaches. Finally, we have provided a perspective on the remaining challenges for high-resolution atlasing and segmentation of the subcortex, which we believe will eventually be tackled with modern ML techniques.

Some of the limitations of our work revolve around the fact that there exists a large variety of segmentation protocols between studies and groups (e.g., Yushkevich et al., 2015a). While we acknowledge that it is a key aspect for atlasing and segmentation methods, it is unfeasible to list the associated protocols for all the surveyed works and we refer the reader to the original publications for more detailed information. Moreover, protocol differences prevent us to provide a direct and fair comparison between the metrics reported by the segmentation methods, something that can be overcome by, for example, the organisation of subcortical segmentation challenges where the same protocol is used for all participants. Another limitation is that, while connectivity-based techniques are important in the study of the subcortex, we are mostly centred to morphometric studies. Finally, despite the effort on covering the whole spectrum of subcortical studies, we recognise that some bias may be found on the surveyed works due to the authors' background.

While the human subcortex remains unexplored to a fair extent, advances in imaging (e.g., MR acquisition, histology reconstruction, and even other modalities like optical coherence tomography) are enabling 3D imaging of this region with increased resolution and contrast. Combined with a positive shift in the culture of data sharing, these enhanced images will allow scientists around the world to describe the subcortex with an unprecedented level of detail. We believe that this will be a multidisciplinary effort that will involve neuroimaging and ML experts, who will combine high-resolution atlases with novel ML algorithms to push the boundaries of our understanding of the subcortex.

Data availability coding

The manuscript reviews the literature on brain atlases and *in-vivo* segmentation methods and discusses the op- portunities and challenges that high-resolution atlases and machine learning bring to in-vivo segmentation of the hu- man brain. As such, we do not use any concrete data nor code.

Credit authorship contribution statement

Adrià Casamitjana: Conceptualization, Methodology, Writing – original draft, Writing – review & editing. **Juan Eugenio Iglesias:** Conceptualization, Methodology, Writing – original draft, Writing – review & editing.

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