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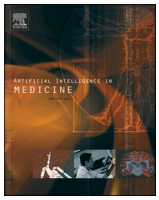

Review on deep learning fetal brain segmentation from Magnetic Resonance images

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ABSTRACT

Brain segmentation is often the first and most critical step in quantitative analysis of the brain for many clinical applications, including fetal imaging. Different aspects challenge the segmentation of the fetal brain in magnetic resonance imaging (MRI), such as the non-standard position of the fetus owing to his/her movements during the examination, rapid brain development, and the limited availability of imaging data. In recent years, several segmentation methods have been proposed for automatically partitioning the fetal brain from MR images. These algorithms aim to define regions of interest with different shapes and intensities, encompassing the entire brain, or isolating specific structures. Deep learning techniques, particularly convolutional neural networks (CNNs), have become a state-of-the-art approach in the field because they can provide reliable segmentation results over heterogeneous datasets. Here, we review the deep learning algorithms developed in the field of fetal brain segmentation and categorize them according to their target structures. Finally, we discuss the perceived research gaps in the literature of the fetal domain, suggesting possible future research directions that could impact the management of fetal MR images.

1. Introduction

Fetal magnetic resonance imaging (MRI) is a non-invasive diagnostic tool that characterizes the development of the central nervous system and contributes to pregnancy management [1,2]. Over the last two decades, its use has spread widely owing to advances in imaging and analysis technologies. In this scenario, even though ultrasound remains the primary imaging modality in the examination of fetal development, MRI can play a crucial role in disentangling doubtful diagnoses owing to its superior image resolution and tissue contrast [3].

Neuroimaging studies have increasingly gained importance in the evaluation of brain growth and development during the fetal period owing to an increasing number of detailed images of the fetal brain acquired at the sub-millimeter scale. In these studies, brain structure segmentation is an essential prerequisite for identifying and labeling brain regions and deriving more accurate quantitative measurements. Although manual segmentation is time-consuming and prone to high intra- and inter-observer variability, automatic segmentation promises efficiency and reproducibility [4]. Consequently, latest research have begun to deepen artificial intelligence (AI)-based approaches to automatically segment different tissue compartments with the aim of making this process operator-independent [5,6].

The recent studies on image segmentation are almost exclusively based on deep learning (DL) approaches, which implement multiple processing layers to extract representations from data by mimicking the working mechanism of the human brain [7]. In this context,

Abbreviations: DL, Deep Learning; CNN, Convolutional Neural Network; FCN, Fully Convolutional Network; MRI, Magnetic Resonance Imaging; SNR, Signal-to-Noise Ratio; FOV, Field Of View; DSC, Dice Similarity Coefficient; GA, Gestational Age; ROI, Region Of Interest; CB, Cerebellum; WM, White Matter; GM, Gray Matter; cGM, cortical Gray Matter; dGM, deep Gray Matter; LV, Lateral Ventricles; BS, Brain Stem; CSF, CerebroSpinal Fluid; eCSF, external CerebroSpinal Fluid; vCSF, ventricular Cerebrospinal Fluid; CP, Cortical Plate; BGT, Basal Ganglia and Thalami.

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convolutional neural networks (CNNs), particularly the U-Net [8] architecture, have become the baseline networks that are frequently modified for better segmentation performance [9]. However, novel DL trends such as transformers [10], and in particular their incorporation into CNN-based networks, have proven their potential in the domain of computer vision by improving segmentation performance and decreasing computational complexity [11]. This combined solution enables the extraction of both local and long-range dependencies from images, facilitating the learning of complex correlations between signals [12]. In this way, the segmentation task is performed in few seconds owing to the parallel computation capabilities of graphics processing units, which can speed up the computation performance, allowing almost real-time task execution. DL methods are virtually model-free because they learn to perform tasks directly from training samples. Consequently, their performance can be systematically enhanced as they are fed with more training data.

This study aimed to provide a comprehensive review of the DL techniques used for automatic segmentation of the fetal brain. In 2018, Makropoulos et al. [13] presented segmentation techniques developed for fetal and neonatal brains, with a greater focus on the latter. Recently, Meshaka et al. (2022) [14] presented a scoping review summarizing the current state-of-the-art and emerging AI trends in fetal MRI. In particular, their review covered a wide range of AI algorithms applied to the entire fetal imaging context, including pre-processing, post-processing, and data interpretation (i.e., disease classification and prognosis). Conversely, we conducted an in-depth investigation of the literature focusing on a specific topic and methodology, that is, the segmentation of the brain from fetal MR images using DL-based algorithms. DL has quickly become the benchmark approach for image segmentation tasks. We considered a wide range of DL-based approaches and categorized them according to their main aims: brain extraction, brain structure segmentation, multi-tissue annotation of the whole brain, and miscellaneous applications. The identified approaches were sorted in chronological order, and studies by the same first author were presented consecutively. In this way, a comparison among the algorithms was facilitated, and the readers were supported in the identification of the solution that best fits their fetal processing pipeline.

1.1. Image acquisition and pre-processing

Fetal MRI examination is currently performed using a 1.5 T or 3 T MRI scanner with an abdominal or cardiac phase-array coil without exceeding the SAR limit of 2 W/kg for maternal whole-body exposure imposed by the Food and Drug Administration [2]. 3 T scanners are associated with more artifacts (i.e., standing wave, conductivity, and susceptibility artifacts); nonetheless, their superior signal-to-noise ratio (SNR) encourages the use of advanced techniques such as susceptibility weighted imaging, MRI spectroscopy, diffusion tensor imaging, and resting-state functional MRI [2,15].

Fetal brain MR acquisition sequences must be extremely fast to capture the entire brain, as neither maternal nor fetal sedation is used, and the fetus can move freely during the entire examination. Among different MRI sequences, the standard anatomical protocol usually includes the following:

- T2-weighted (T2w) single-shot fast or turbo spin-echo sequences (i.e., Siemens HASTE, GE SS-FSE, Philips SSH-TSE/UFSE), which represent the pillar of fetal MRI as they allow to minimize fetal movement artifacts by acquiring each slice at a time. This approach ensures that the movement-related artifacts are confined solely to those slices acquired during periods of fetal motion. T2w images are usually characterized by a high in-plane resolution of 0.4–1 mm, with a large slice thickness of 2–4 mm [2,16,17] to improve the SNR. Thus, it is crucial to acquire these sequences in all three orthogonal planes (axial, coronal, and sagittal) relative to the fetal head with no interslice gap. The field of view (FOV) generally ranges from 240 mm to 350 mm to ensure brain acquisition, even if the fetus is moving during the acquisition (Fig. 1).
- Balanced steady-state gradient echo sequences (i.e., Siemens TRUE-FISP, GE FIESTA, Philips b-FFE), which are increasingly gaining popularity in the fetal MRI field. These sequences may be acquired with reduced thickness [2,16,17] and acquisition times [16] compared to T2w sequences. Furthermore, these sequences are useful for their improved characterization of smaller structures (e.g., vascular structures [18] and cranial nerves [2]), which exhibit more defined anatomical details (Fig. 1). However, these sequences are usually characterized by the presence of artifacts owing to their susceptibility to field inhomogeneities (e.g., Fig. 2, box B) [16] and/or by the presence of artifacts at the tissue interfaces close to the gastrointestinal tract [19]. The presence of intensity artifacts may be a critical source of errors in any segmentation operation performed on these images. Moreover, these sequences exhibit a reduced tissue-to-contrast ratio between tissues with similar T2 to T1 ratios [19] and/or when ultrashort repetition times are used to shorten the acquisition duration [16].

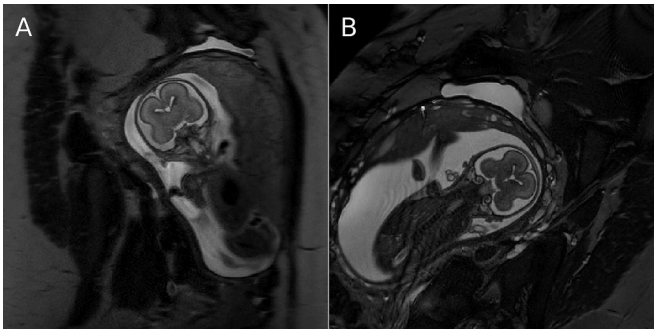

Fig. 1. Example of T2w turbo spin-echo (TSE, A) and balanced fast field echo (b-FFE, B) sequences. Both sequences are reported in the coronal orientation. In detail, the TSE sequence is characterized by an in-plane resolution of 0.47 mm^3, a FOV of 240 mm, and an echo and repetition time of 180 ms and 3500 ms; the b-FFE sequence is characterized by an in-plane resolution of 0.71 mm^3, a FOV of 250 mm and an echo and repetition time of 4.6 ms and 9.5 ms.

Ultrafast 2D sequences with anisotropic voxels are preferred to 3D sequences because of their lower susceptibility to fetal movement and higher SNR [20,21]. Furthermore, novel advanced super-resolution algorithms can handle multiple 2D fetal scans, possibly corrupted by motion artifacts, and generate high-resolution fetal brain reconstructions with an isotropic voxel size. Existing 3D fetal brain reconstruction frameworks, such as NiftyMIC[1] [22], MIALSRTK[2] [23], and SVRTK[3] [24], generally rely on three main steps [25]: global registration of the scans in the masked brain region followed by the generation of an average initial 3D image, rigid registration of each slice to the 3D image (an exhaustive survey of existing approaches can be found in [26]), and super-resolution reconstruction of the 3D image with outlier rejection [23,24,27,28]. The latter two steps were iteratively repeated several times to ensure convergence into a stable solution.

Pre-processing operations applied to images before feeding them to segmentation tools improve their quality and enhance the specific features involved in the analysis. There are several pre-processing techniques adopted on images, and the most common are intensity correction and brain extraction.

Intensity inhomogeneity correction targets the removal of intensity

[1] https://github.com/gift-surg/NiftyMIC

[2] https://github.com/Medical-Image-Analysis-Laboratory/mialsuperresolutiontoolkit

[3] https://github.com/SVRTK/svrtk-docker-gpu

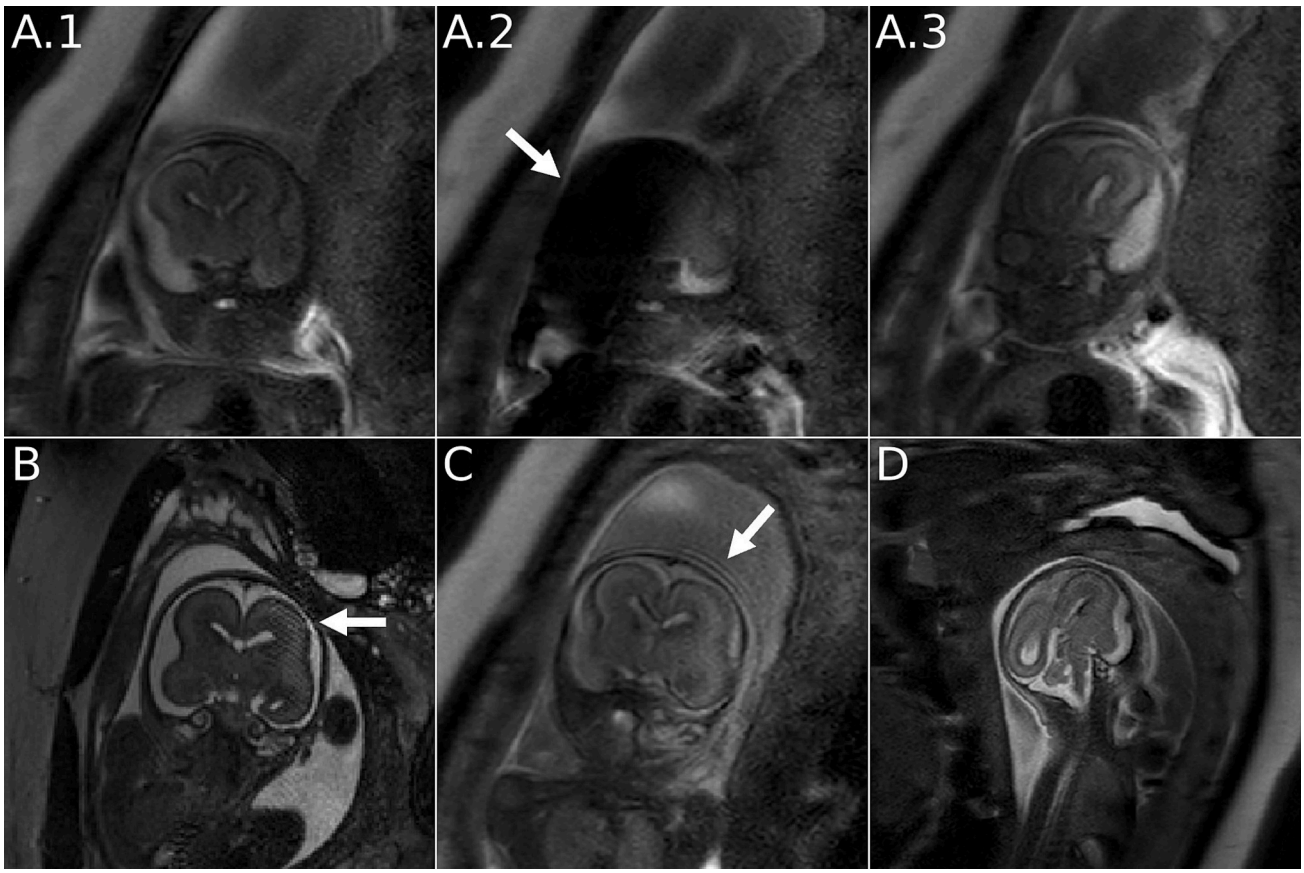

Fig. 2. Artifacts on fetal MR images. Motion artifacts are visible in consecutive acquired slices (A.1 - A.3). Intensity artifacts, ringing artifacts, and no standard acquisition orientation effects are visible in boxes B, C, and D, respectively.

bias, that is a low spatial frequency artifact superimposed to the acquired image. This can be applied either before or during the segmentation process. The N4 algorithm [29] is usually applied to perform intensity inhomogeneity corrections in perinatal brain imaging [13]. Other approaches benefit from data augmentation to render networks invariant to intensity inhomogeneities. In this context, a well-established approach is intensity inhomogeneity augmentation [30], which exploits the application of multiple linear gradients with random offsets and orientations to each image, free from intensity inhomogeneity artifacts.

Tissue and structural segmentation methods often involve brain extraction prior to processing. In this review, we outline brain extraction techniques as a special category of segmentation methods and describe them in Section 3.1. Few methods have been developed for segmenting the brain tissue using a 3D approach. In such cases, the pre-processing pipeline usually includes the reconstruction of a high-resolution volume with an isotropic voxel size from the acquired images, with correction of the relative displacement among slices. To reconstruct the fetal brain as accurately as possible, at least one sequence per orthogonal orientation is recommended [28,31].

1.2. Challenges in fetal brain MRI segmentation

Automatic human brain segmentation from MR images is a challenging task for the accurate detection of the structures and tissues required for the extraction of quantitative imaging biomarkers. The unpredictable positions of the patient and motion artifacts complicate accurate delineation of tissue boundaries. Radiofrequency excitation field inhomogeneity, non-uniform reception coil sensitivity, eddy currents driven by field gradients, and electromagnetic interactions with the body [32,33] can cause intensity inhomogeneities of different tissue classes over the image space. Additionally, partial volume (PV) effects, which arise when a mixture of signals from multiple tissue types occurs in a single voxel, generate mislabeled segmentation.

The domain-specific challenges in automatic fetal brain segmentation from MR images are:

- Increased occurrence of motion artifacts (i.e., spontaneous movement of the fetus and maternal breathing) compared with the context of the born subject. Motion during image acquisition can lead to various types of artifacts, such as in-plane image blur, slice crosstalk, incongruence in the relative location among slices, and spin-history artifacts, which can considerably affect the image quality of individual slices (Fig. 2).
- Low contrast-to-noise ratio caused by the small size of the fetal brain and shorter scanning periods of the acquired sequences [34].
- Acquisition limits (i.e., thick slices) to achieve a good SNR. A poor SNR causes difficulties in accurately delineating brain tissue boundaries.
- Low tissue contrast. In fetal images, the intensity difference between the white matter (WM) and gray matter (GM) is reduced due to 1) the lack of myelin in the WM in the fetal brain and 2) cerebrospinal fluid (CSF) - WM partial volume effects. The fetal brain MR images exhibited an inverted WM/GM contrast compared with the adult data. The WM, which is predominantly unmyelinated in the fetal brain, appears brighter than the GM on T2w images. The mixing of the CSF and GM in the CSF - cortical GM (cGM) boundary leads to intensities similar to the intensity profile of the WM. This partial volume effect leads to mislabeling of voxels in the CSF-cGM interface as WM [35].
- Rapid and complex cerebral changes in shape, appearance, and function occur during pregnancy. This causes unequivocal

difficulties in defining and identifying the different brain structures. This is the case for neuronal migration from the germinal matrix toward the cerebral wall to form a prospective neocortex. During this process of corticogenesis, the fetal brain undergoes intensive laminar organization [36].

- Lack of manually labeled data accounting for different pathologies and congenital disorders, potentially acquired on different scanners, to be used as paradigms for automatic segmentation algorithms [37]. Manual delineation of detailed structures requires expert anatomical knowledge and is a time-consuming task prone to human error.

2. Methods

The review was first performed on May 2022, and an updated repeat search was performed on February 2023 by one investigator using appropriate research terms relating to *"fetus," "MRI,"* and *"deep-learning"* (see Supplementary Material) within the bibliographic database of PubMed, Web of Science, and Scopus. Furthermore, to identify all evidence relevant to the research questions, a manual search was performed using the Google search engine. All included articles were peer-reviewed in English, without any predefined date limits or restrictions on sample size.

The exclusion criteria for the current review applied to the retrieved articles were:

- studies not including fetal participants;
- sample data not MRI-related (i.e., ultrasound imaging);
- articles not describing DL methods for automated segmentation;
- methods not segmenting the fetal brain.

Furthermore, case reports, review articles, and opinion pieces were excluded from the results, although their reference lists were manually assessed for important additional references. The search strategy yielded 1831 studies (PubMed, $n = 266$; Scopus, $n = 1391$; Web of Science, $n = 1069$). After checking for duplicates and screening titles and abstracts, we identified 253 potential articles, 18 of which emerged from a more extensive manual search using the Google search engine. Thirty-nine studies were included in this review based on inclusion and exclusion criteria. The study selection process is illustrated in Fig. 3.

In this review, the analyzed segmentation techniques are categorized according to their main aim: brain extraction, main brain structures segmentation, and multi-tissue annotation of the whole brain (Fig. 4). These methods are typically adopted for facilitating further quantitative analysis such as brain volumetric measurements. In particular, brain extraction methods produce a mask of the whole brain, thereby removing the skull and non-brain structures from the MR image. Structural segmentation methods delineate one or few structures of interest in the brain, but without whole-brain coverage. Multi-tissue brain annotation algorithms label each voxel of the brain according to a predefined list of brain structures, thus covering the whole-brain anatomy. Furthermore, a separate section is dedicated to miscellaneous applications, in which the reported studies show interesting brain extraction or structure segmentation techniques applied with a different purpose than brain segmentation per se.

3. Results

Table 1 overviews the characteristics of each segmentation method discussed in this review, grouped by their common strategy. All the methods included were compared in terms of the Dice similarity coefficient (DSC), which is the only common metric to assess segmentation accuracy. The DSC measures the amount of overlap between the manual annotations, referenced as the "gold standard" (GS), and the segmentation generated by the method (MS). It is defined as

$$\mathrm{DSC} = 2^{*}\frac{|\mathrm{MS} \cap \mathrm{GS}|}{(|\mathrm{MS}| + |\mathrm{GS}|)}$$

The DSC takes a value of 1 in the case of a perfect match between the

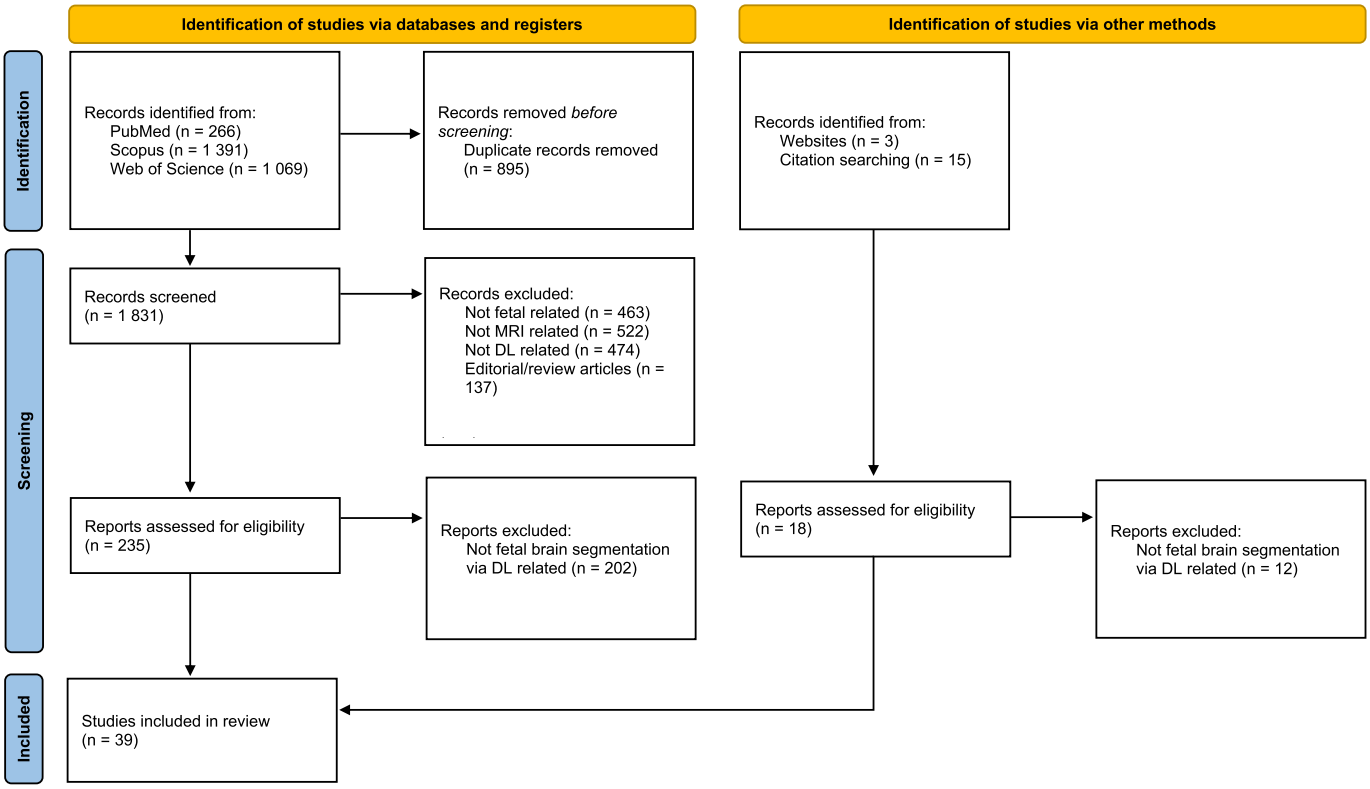

Fig. 3. PRISMA flow diagram. It reports the study selection process adopted in this review.

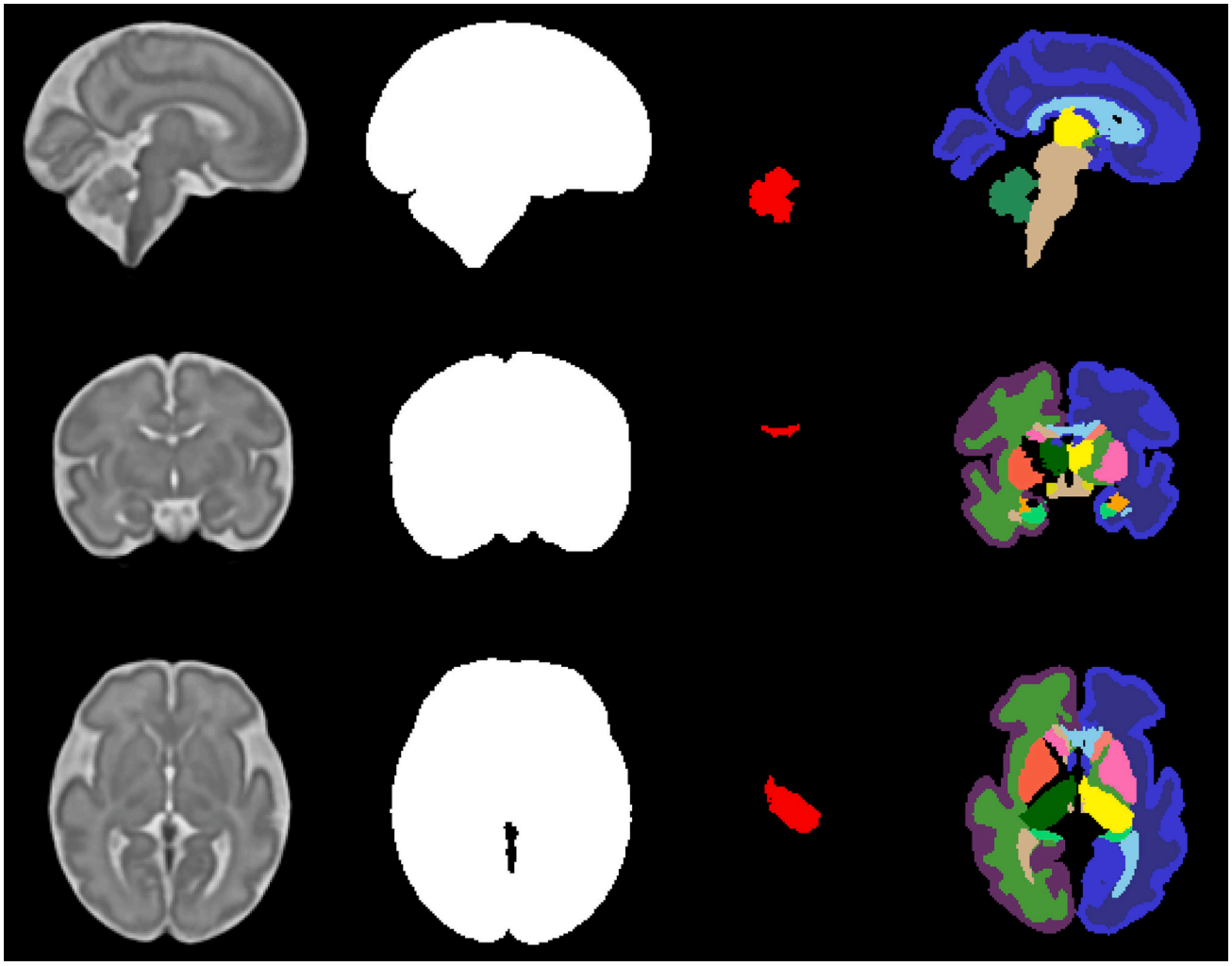

Fig. 4. Segmentation techniques. Examples of the application of the different segmentation techniques in all three orthogonal orientations (sagittal, coronal, and axial), treated in this review: brain extraction, brain structure segmentation, and brain multi-tissue annotation. From left to right: MR image, brain extraction (reported in white), brain structures segmentation (cerebellum, corpus callosum, and left thalamus, respectively reported in red from top to bottom), multi-tissue annotation (multiple colors). These images are extracted from the spatiotemporal atlas [38] of normal brains at 33 weeks of gestation. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

two segmentations and 0 when there is no overlap. However, the DSC scores obtained from different segmentation studies may not be directly comparable because they may have been computed from different datasets. Although other metrics exist to evaluate segmentation results [39], DSC remains the most frequently used measure. Table 2 lists only those articles included in this review that report details about the public availability of the datasets and/or of the proposed algorithms.

3.1. Brain extraction

Brain extraction is used to remove the skull from head MR scans and preserve only the cerebral tissues. This is an intermediate albeit main step in image processing and has a major impact on further processing and analysis.

In the fetal context, the brain must be separated from the maternal tissue, thus complicating the operation. To address this problem, several methods include a preliminary fetal brain localization step to guide brain extraction. Hereafter, two approaches are presented: fetal brain extraction from the full FOV, or after a brain localization step.

3.1.1. Brain extraction guided by brain localization

Rajchl et al. (2017) [40] proposed DeepCut as an extension of GrabCut [77]. DeepCut uses a LeNet-inspired architecture [78], followed by a densely connected conditional random field (CRF). The net is trained using bounding box segmentation provided as input rather than manual segmentation of the whole brain. DeepCut iteratively updates the training targets learned by the net and employs the densely connected CRF to regularize the segmentation.

Salehi et al. (2017) [41] introduced an auto-context algorithm [79] coupled with CNNs capable of performing brain extraction from MRI. Although the method is originally developed to extract brains from images of born subjects, it is also evaluated in the fetal context by including a preliminary bounding box annotation of the brain manually defined using ITKSNAP [80]. In particular, the authors evaluated two architectures: Auto-2.5D-CNN and Auto-U-Net. Auto-2.5D-CNN consists of three parallel 2D convolutional pathways, one for each orthogonal orientation (axial, coronal, and sagittal), whose inputs are 2D patches of three different sizes, as proposed by [81], to include 3D information intrinsically. By contrast, Auto-U-Net comprises three 2D fully convolutional networks (FCNs), one for each orthogonal orientation, based on the original U-Net architecture [8]. In both architectures, the outputs of the three pathways are combined to provide the final brain mask.

Wang G. et al. (2018) [42] proposed an interactive segmentation framework (BIFSeg) with image-specific fine-tuning that is capable of

Table 1
Summary of the main characteristic of the reviewed articles. "Performance" is expressed in terms of Dice score (the most common performance index) of the best solution reported in the original article. "Samples" reports all volumes/subjects included in the study, eventually split according to the manuscript criteria.

Author	Method	Type	Samples	Gestational Ages (weeks)	Performance (Dice Score)
Brain extraction guided by brain localization					
Rajchl et al. 2017 [40]	DeepCut	3D	55 subjects	20–30	94.10 %
Salehi et al. 2017 [41]	Auto-2.5D-CNN Auto-U-Net	2D	75 volumes	19–39	95.97 % 93.80 %
Wang G. et al. 2018 [42]	BIFSeg	2D	18 subjects	–	95.58 %
Lou et al. 2019 [43]	DS U-Net	2D	123 volumes	–	91.68 %
Li J. et al. 2020 [44]	multi-scale FCN	2D	88 subjects	20–30	95.80 %
Dudovitch et al. 2020 [45]	Two-step U-Nets	3D + 2D	35 volumes	–	96 %
Liao et al. 2020 [46]	multi-stage U-Net	2D	DBa: 178 volumes DBb: 123 volumes	DBa: 21–36 DBb: -	DBa: 95.79 % DBb: 95.45 %
Wang G. et al. 2020 [47]	UGIR	2D	105 volumes	2nd trimester	91.82 %
Chen J. et al. 2021 [48]	DU-Nets	3D	77 subjects	23–34	98.23 %
Zhang et al. 2021 [49]	Confidence-aware Cascaded Net	2D	239 volumes	23–34	95.77 %
Unguided brain extraction					
Khalili et al. 2017 [50]	Multi-scale CNN	2D	DBax: 10 subjects DBcor: 10 subjects DBsag: 10 subjects	22.9–34.6	DBax: 91 % DBcor: 95 % DBsag: 92 %
Salehi et al. 2018 [51]	Auto-U-net	2D	285 volumes	22–38	HS: 96.52 % ChS: 78.83 %
Khalili et al. 2019b [52]	Joint U-net	2D	DBa: 45 volumes DBb: 17 volumes	DBa: 23–35 DBb: 29 ± 5	DBa: 98 % DBb: 94 %
Rampun et al. 2019 [53]	Deep U-Net	2D	200 volumes	18–37	92.80 %
Rampun et al. 2020 [54]	*Hybrid-Nets* FS-R2-U-Net (HS) FS-Att-U-Net (PSab)	2D	HS: 200 volumes PSab: 74 volumes	18–38	HS: 89.41 % PSab: 86.21 %
Rampun et al. 2021 [55]	SIMOU-Net	2D	HS: 200 volumes PSab: 54 volumes	18–39	HS: 94.2 % PSab: 91.2 %
Gu et al. 2021 [56]	CA-Net	2D	36 subjects	22–29	95.88 %
Torrents-Barrena et al. 2021 [57] ˆ	DeepLabV3+	2D	60 volumes	17–37	79 %
Faghihpirayesh et al. 2022 [58]	RFBSNet	2D	152 volumes	22–38	HS: 97.99 % ChS: 84.04 %
Rutherford et al. 2022 [59]	CNN auto-mask	2D	DBa: 197 subjects DBb: 10 subjects	DBa: 24–39 DBb: 30–36	DBa: 94 % DBb: 89 %
De Asis-Cruz et al. 2022 [60]	FetalGAN	3D	64 subjects	25–39.4	97.3 %
Sun et al. 2022 [61]	MSMHA-CNN	3D	DBa: 20 subjects DBb: 10 subjects	DBa: 23–34 DBb: 26–34	DBa: 94.78 % DBb: 96.71 %
Brain structure segmentation					
Payette et al. 2019 [62]	Auto-U-Net	2D	HS: 15 volumes PSsb: 15 volumes PSsbas:16 volumes	HS: 23 PSsb: 24.4 PSsbas: 30.1	*LV* HS: 91 % PSsb: 94 % PSsbas: 91 %
Fetit et al. 2020 [63]	multi-scale 3D Deep CNN	3D	249 volumes	21–38	GM: 84 %
Hong et al. 2020 [64]	MVT-FCN	2D	52 subjects	22.9–31.4	CPleft: 90.7 % CPright: 90.6 %
Dou et al. 2021 [65]	Deep attentive CNN	3D	57 subjects	16–39	CP: 87 %
Dumast et al. 2021 [66]	TopoCP	2D	33 subjects	21–38	CP: 70 %
Fidon et al. 2021b [67]	multi-class nnU-Net-DRO	3D	HS: 193 volumes PSsb: 124	19–40	*HS* WM 93.8 %, LV 87.9 %, CB 94.4 % *PSsb*

(*continued on next page*)

Table 1 (*continued*)

Author	Method	Type	Samples	Gestational Ages (weeks)	Performance (Dice Score)
			volumes PSab: 51 volumes		WM 90.3 %, LV 90.9 %, CB 79.7 % *AC* WM 90.3 %, LV 87.5 %, CB 90.6 %
Multi-tissue annotation					
Khalili et al. 2019 [30]	multi-class U-Net	2D	12 subjects	22.9–34.6	*AVERAGE: 88.4 %* CB: 80.2 %, BGT: 88.9 %, vCSF: 87.5 %, WM: 92.2 %, BS: 93.0 %, cGM: 82.9 %, eCSF: 94.3 %
Payette et al. 2020 [68]	multi-class U-Net	2D	15 subjects HS: 18 subjects	22.6–33.4	*AVERAGE*: 86 %*
Payette et al. 2021 [37] (FeTA Challenge 2020)	KispiU SeBRe IBBM	2D	PSsb: 32 subjects PSsbas: 32 subjects	20–33	*
Fidon et al. 2021 [69]	3D U-Net	3D	HS: 168 volumes PSsb: 96 volumes	20–35	*AVERAGE: 74.8 %* WM: 91.5 %, LV: 90.7 %, CB: 89.6 %, eCSF: 75.3 %, cGM: 56.6 %, dGM: 71.4 %, BS: 61.5 %, CC: 62.0 % *AVERAGE*: 89.7 %
Zhao L. et al. 2022 [70]	multi-class 3D U-Net	3D	106 volumes	24.4–39.4	CSF: 92.2 %, cGM: 82.8 %, WM: 90.8 %, dGM: 88.4 %, CB: 93.5 %, BS: 90.2 %
Karimi et al. 2023 [71]	multi-class nnU-Net	3D	294 subjects	19.6–38.9	*AVERAGE*:* *Young (GA < 32): 89.3 %* *Older (GA ≥32): 91.6 %* *AVERAGE*: 83.79 %
Huang et al. 2023 [72]	CoT-CNN	3D	80 volumes	20–35	eCSF: 85.49 %, GM: 71.20 %, WM: 89.73 %, LV: 86.38 %, CB: 85.75 %, dGM: 84.64 %, BS: 83.31 %
Payette et al. 2023 [73] (FeTA Challenge 2021)	21 different networks	2D/3D	HS: 33 subjects PSsb: 47 subjects	20–35	*
Miscellaneous application: brain extraction or structure segmentation as part of a processing pipeline					
Ebner et al. 2018 [74]	coarse-to-fine CNN	2D	HS: 30 subjects PSsb: 16 subjects PSsbas: 16 subjects	HS: 30 ± 5 PSsb: 24 ± 1 PSsbas:26 ± 1	PSsb: 93.87 % PSsbas: 92.94 %
Ebner et al. 2020 [22]	coarse-to-fine CNN	2D	HS: 37 subjects PSsb: 32 subjects PSsbas: 16 subjects	HS: 27 ± 4 PSsb: 23 ± 2 PSsbas:26 ± 1	HS: 93.21 % PSsb: 93.87 % PSsbas: 92.94 %
Li H. et al. 2021 [75]	2D U-Net	2D	636 volumes	21–40	97 %
Avisdris et al. 2021 [76]	multi-class U-Net	2D	214 volumes	22–39	CB: 85.1 % LH: 94.5 % RH: 94.6

Healthy Subjects (HS); Challenging Subjects (ChS); Pathological Subjects (PS): spina bifida (sb), spina bifida after surgery (sbas), abnormal (ab)
axial (ax); coronal (cor); sagittal (sag);
Cerebellum (CB); White Matter (WM); Gray Matter (GM); cortical Gray Matter (cGM); deep Gray Matter (dGM); Lateral Ventricles (LV); Brain Stem (BS); CerebroSpinal Fluid (CSF); external CerebroSpinal Fluid (eCSF); ventricular CerebroSpinal Fluid (vCSF), Corpus Callosum (CC), Cortical Plate (CP), Basal Ganglia and Thalami (BGT), Left and Right Hemisphere (LH, RH), Database (DB)
*Detailed scores are reported on diagrams in the original paper; ˆmultiple networks are reported in the original paper.

segmenting the fetal brain. This framework consists of a CNN based on the P-Net [82] structure, which takes the content of a manually defined brain bounding box as input and extracts the brain accordingly. In addition, the image-specific fine-tuning step included in this framework refines the segmentation "on the fly" using unsupervised (without additional user interactions) or supervised (with user-provided scribbles) approaches.

In a subsequent study, Wang G. et al. (2020) [47] proposed an uncertainty-guided interactive refinement (UGIR) framework for fetal brain extraction. The framework consists of two modules: a multiple-group convolution-based CNN (MG-Net) [8,83] that simultaneously obtains an initial brain extraction with its uncertainty estimation, and an interaction-based method for the fast refinement of brain extraction [84].

Lou et al. (2019) [43] introduced a multistage 2D U-Net with deep supervision (DS U-Net) for fetal brain extraction. This approach consists of three main steps: coarse segmentation to define a 3D bounding box of the brain, further segmentation to produce finer brain extraction, and a final refined segmentation based on a local patch strategy. Each step employs the same U-Net architecture [8] trained with a deep supervision loss computed as the weighted sum of the overall loss and companion losses associated with all intermediate layers.

Li J. et al. (2020) [44] proposed a two-step framework for extracting the fetal brain from MRI slices. This framework consists of two 2D FCNs [85] that employ dilated convolutional layers to increase the receptive field: a shallow FCN that rapidly locates the fetal brain in each MRI slice and extracts the region of interest (ROI) containing the brain, and an extra-deep multi-scale FCN including residual blocks that further refines

Table 2
Publicly available software and their training datasets for fetal brain segmentation from MR images.

Segmentation software	Public Dataset	Available code
Brain extraction guided by brain localization		
Wang G. et al. 2020 [47]	–	https://github.com/HiLab-git/UGIR
Chen J. et al. 2021 [48]	–	https://github.com/JamesC0321/fetal_brain_extraction
Unguided brain extraction		
Salehi et al. 2018 [51]	–	bitbucket.org/bchradiology/u-net
Gu et al. 2021 [56]	–	https://github.com/HiLab-git/CA-Net
Rutherford et al. 2022 [59]	https://openneuro.org/datasets/ds003090/versions/1.0.0	https://github.com/saigerutherford/fetal-code
Sun et al. 2022 [61]	–	https://github.com/sunmoon91/MSMHA
Brain structure segmentation		
Fetit et al. 2020 [63]	–	https://github.com/afetit/fetal-mri-segmentation
Dou et al. 2021 [65]	–	https://github.com/bchimagine/FetalCPSeg
Fidon et al. 2021b [67]	https://www.cir.meduniwien.ac.at/research/fetal	https://github.com/LucasFidon/HardnessWeightedSampler
Multi-tissue annotation		
Payette et al. 2021 [37] (FeTA Challenge 2020)	https://www.synapse.org/#!Synapse:syn23747212/files/	https://github.com/itsasimiqbal/SeBRe
Fidon et al. 2021 [69]	–	https://github.com/LucasFidon/fetal-brain-segmentation-partial-supervision-miccai21
Payette et al. 2023 [73] (FeTA Challenge 2021)	https://www.synapse.org/#!Synapse:syn25649159/files	https://hub.docker.com/u/fetachallenge
Miscellaneous application: brain extraction or structure segmentation as part of a processing pipeline		
Ebner et al. 2018 and 2020 [22,74]	–	https://github.com/gift-surg/NiftyMIC

the segmentation.

Dudovitch et al. (2020) [45] proposed a DL method trained using a few annotated scans to extract the fetal brain. This method employs two types of CNNs: a custom 3D U-Net architecture [86,87] and a 2D U-Net [8]. The first allows bounding box definition and brain extraction, whereas the second is devoted to the correction of the segmentation of the brain slices that are most prone to error by taking into account the segmentation results of adjacent slices.

Liao et al. (2020) [46] proposed a multistage DL model for joint image quality assessment and fetal brain extraction from MR images. The model includes brain detection (bounding box stage), feature extraction, and a task-specific module (brain extraction and quality assessment). Both the brain detection and feature extraction modules are based on the U-Net architecture [8]. However, the second module presents additional deformable convolutional layers that adaptively adjust the receptive field to deal with variable brain shapes. The task-specific module contains two separate convolutional sub-networks to extract the brain and assess image quality.

Chen J. et al. (2021) [48] suggested a 3D DL-based and multi-step framework for brain extraction from fetal MR images. The framework consists of a global localization network that estimates probability maps for brain candidates, a local refinement network that produces finer brain extraction probability maps, and a final convolutional fusion network that derives results using the two cascaded probability maps obtained from the previous two steps. In detail, a 3D densely connected U-Net [88] is used in both global localization and local refinement networks.

Zhang et al. (2021) [49] proposed a confidence-aware cascaded framework for extracting fetal brain from MR images. The framework consists of two modules based on the original U-Net architecture [8]: a localization module to coarsely extract and localize the fetal brain slice by slice, and a fine module to improve segmentation. The advantage of this framework is the computation of a slice-specific confidence level for brain extraction at the end of the localization module. The confidence scores are used as input in the fine module, which uses the slices that achieved high confidence scores to guide brain extraction in the slices that achieved low confidence scores (e.g., blurred boundaries). Because the framework relies on a slice-wise approach, slice consistency loss is adopted to enhance the consensus between the segmentation of adjacent slices.

3.1.2. Unguided brain extraction

Khalili et al. (2017) [50] presented a multiscale CNN for segmenting the fetal brain from MR images. The network, developed from the architecture proposed in [81], consists of three parallel 2D convolutional pathways combined in the last fully connected layer. Each branch analyzes 2D patches of different sizes to gather information from both local and global contexts of interest.

In a subsequent study, Khalili et al. (2019b) [52] implemented a 2D CNN to segment the brain for both fetal and neonatal MR scans. The network consists of a smaller version of the original U-Net architecture [8] and is trained with a combination of fetal and preterm neonatal scans acquired in three orthogonal orientations without any pre-processing steps. Furthermore, as in their previous study [50], they exploited a post-processing algorithm based on 3D connected components to prevent erroneous brain-labeled clusters of voxels. Interestingly, the proposed method is trained and tested on different datasets ($n = 3$), including heterogeneous imaging parameters (field strength, image acquisition plane, and image resolution), infant age (23–45 weeks postmenstrual age), and pathologies (post-hemorrhagic ventricular dilatation, stroke, asphyxia, and Down's syndrome).

In 2018, Salehi et al. [51] upgraded their previously proposed Auto-U-Net (developed for adult MRI) [41] to segment the fetal brain directly on each acquired 2D slice without requiring image pre-processing. The proposed network is validated not only in normal cases but also in extremely challenging cases (e.g., motion-corrupted, noised, and abnormally shaped cases).

Rampun et al. (2019, 2020, 2021) [53–55] proposed three different methods for extracting fetal brain from MR images by adopting 2D CNNs based on the original U-Net [8] architecture. In the first work [53], they proposed a deep CNN architecture to capture finer textural information; in the second work [54], they introduced the fusion strategy concept by developing hybrid networks inspired by U-Net and heuristic edge detection [89] architectures; in the third work [55], they developed a single-input multi-output U-Net (SIMOU-Net) architecture that extracts and combines middle-path side outputs to take into account some meaningful side features, thus promoting an ensemble learning strategy. More specifically, the hybrid networks introduced by Rampun et al. (2020) [54] employ the original U-Net [8], Att-U-Net [90], and R2-U-Net [91] as baseline architectures, and incorporate four different fusion strategies based on a combination of multisource, multiscale, multilevel local, and global information without losing spatial information. The SIMOU-Net architecture introduced in the third work is based on a CNN architecture with eight levels of convolutional blocks (vs. five of the original U-Net [8]) that generates five prediction maps (four of them come from the intermediate stages of the decoder and the decoder output). These maps are then aggregated through different

operations, namely “mean”, “median”, and “maximum”, to reduce the variance of prediction and generalization errors.

Gu et al. (2021) [56] proposed a comprehensive attention-based CNN (CA-Net) that is aware of 1) the spatial position of the relevant ROI to suppress erroneous information, 2) the level of relevant feature channels to suppress irrelevant channels, and 3) the most salient feature maps among multiple scales to deal with objects in different scales. The proposed CA-Net presents a U-Net [8] backbone upgraded with four spatial attention modules, four channel attention modules, and one scale attention module. The spatial attention modules are a combination of non-local blocks [92] at the lowest resolution level and dual-pathway attention gates [93] at other resolution levels.

Torrents-Barrena et al. (2021) [57] compared several DL networks for the extraction of fetal brain from MR images, even those that are not specifically developed for the fetal context. The following networks are tested: 3D U-Net [86], V-Net [94], Dense V-Net [95], DeepMedic [96], HolisticNet [97], RefineNet [98], 3D HighResNet [99], BiSeNet [100], PSPNet [101], ResNet [102], DeepLabV3+ [103], Pix2Pix [104], Tiramisu [105] and DenseASPP [106].

Faghihpirayesh et al. (2022) [58] proposed a real-time fetal brain segmentation network (RFBSNet) from MR images. RFBSNet is a CNN-based network that uses a U-Net style [8] architecture with forward connections to retain accuracy and a two-branch architecture to achieve fast inference. In particular, the two-branch architecture presents an input downsampling module that reduces the input image size, providing high-resolution spatial information to the final classification module (i.e., the softmax layer) through a forward path.

Rutherford et al. (2022) [59] proposed the first CNN method to automatically extract fetal brain from functional MRI (fMRI) data. Compared to structural data, functional data are characterized by a lower spatial resolution and SNR. Furthermore, motion across consecutive volumes can be larger than is usually expected for adult fMRI acquisition, making it difficult to combine multiple volumes to improve the SNR. The authors proposed a CNN model adapted from the Auto-U-Net architecture [51] specifically trained on fetal fMRI data.

De Asis-Cruz et al. (2022) [60] introduced an end-to-end generative adversarial network (GAN) to extract the fetal brain from resting-state functional MRI (rs-fMRI). The architecture consists of a generator based on a 3D U-Net [94] and a discriminator based on a fully convolutional network [107]. The network is trained using a multiscale loss function that enables both the generator and discriminator to learn hierarchical features (local and global) and capture the relationship between voxels, particularly in the low-contrast regions around the boundary between the fetal brain and maternal tissue.

Sun et al. (2022) [61] proposed a 3D multiscale multihierarchy attention convolutional neural network (MSMHA-CNN) for brain extraction from fetal MR images. The multiscale feature learning block extracts multiscale feature maps (i.e., the contextual features of high-resolution in-plane slices and contextual features between slices) to represent 3D MR images. The hierarchy model is exploited for further performance improvement of fetal brain extraction using multi-hierarchy feature maps. Finally, the channel-wise spatial attention feature fusion block is introduced to effectively fuse these learned multiscale and multihierarchy features by adaptively learning their optimal fusion weights at the voxel level.

3.2. Brain structure segmentation

Segmentation of brain structures is used to delineate one or more relevant structures of the fetal brain (e.g., the corpus callosum, ventricles, cerebellum, and vermis). It differs from brain extraction and multi-tissue annotation tasks because it does not consider the brain as a whole, i.e. the structures of interest are not the brain itself and do not cover it entirely. In a broader sense, it can be considered as a branch of the aforementioned tasks; however, we agreed to keep it separate because of the different technical solutions it might undergo. Furthermore, all methods surveyed in this section present common preliminary pre-processing steps aimed at computing a super-resolution volume with an isotropic voxel size from a series of 2D acquired sequences.

Payette et al. (2019) [62] proposed a U-Net-based architecture to segment fetal brain ventricles for longitudinal and volumetric analyses. The architecture adopted is based on Auto-U-Net [51], with the addition of batch normalization layers. Furthermore, the algorithm is trained using a dataset that included normally developing subjects and patients with dilated ventricles who underwent spina bifida correction surgery.

Fetit et al. (2020) [63] proposed an age-invariant DL system to segment the cortical gray matter from the developing fetal brain in MR images. The core of the system is a 3D multi-scale deep CNN developed via a “human-in-the-loop” approach, in which an expert annotator refines segmentation obtained from the model originally trained on automatically generated labels using the Draw-EM algorithm [108]. The proposed 3D architecture is developed using the open-source platform DeepMedic v0.7.0 [109] and is based on multiple parallel convolutional pathways, each processing the input at different resolutions (i.e., at the original, three-times, and five-times downsampled resolutions). The output features of the three pathways are concatenated and processed using the final classification layer.

Hong et al. (2020) [64] introduced a FCN with multiple-plane aggregation to segment the cortical plate of the fetal brain from MR images. Because the proposed FCN is based on the original U-Net architecture [8], they adopted a multi-view aggregation approach to correct the 2D-based results and to account for the 3D nature of the cortical plate. They combined the results from three orthogonal planes to generate a final 3D segment and obtained more robust results by applying a data augmentation technique [110]. Additionally, they employed a hybrid loss function based on the logarithmic Dice loss [111], which employs focal Dice loss to increase the overall performance, and focal boundary Dice loss to increase the boundary accuracy.

Dou et al. (2021) [65] proposed a 3D deep attentive FCN with mixed-kernel convolutions for automatic fetal cortical plate segmentation from MR images. The model consists of a backbone network with an encoder-decoder architecture and forward skip connections that link the encoder stages to the corresponding decoder stages. This architecture ends with a stagewise attention refinement module that leverages two groups of mixed-kernel convolution blocks to capture multiscale contextual information.

Dumast et al. (2021) [66] introduced a topological loss function to train a network capable of segmenting the fetal cortical plate from MR images. The architecture is the original U-Net [8], and the proposed loss function includes a combination of binary cross-entropy and topological loss functions. Topological loss is introduced in the training strategy to enhance the morphological consistency of deep learning-based segmentation of the investigated structure.

Fidon et al. (2021b) [67] proposed an nnU-Net [9] architecture trained with the distributionally robust optimization (DRO) algorithm to identify white matter, ventricles, and cerebellum in both pathological (spina bifida and brain abnormalities) and healthy fetal subjects. DRO is a robust generalization of an empirical risk minimization algorithm based on stochastic gradient descent [9], and is used in most state-of-the-art DL segmentation methods. DRO models the uncertainty in the training data distribution by reweighting the training samples with the lowest performance to obtain a more consistent outcome on the underrepresented subsets of the training set. Therefore, the proposed algorithm trains the segmentation network more effectively when the dataset includes only a few samples from a specific population, such as patients with malformations or rare pathologies.

3.3. Multi-tissue annotation

The multi-tissue annotation task includes methods that assign a label to each voxel of an image, thereby splitting the brain into different structures. Most of the proposed methods are developed for 3D high-

resolution images reconstructed from a series of 2D acquired sequences, similar to the structure segmentation task. The purpose of the multi-tissue annotation task is to extend the brain segmentation task by distinguishing between all brain structures. However, one of the major challenges in this task is the limited availability of public datasets for network training. A large amount of manually annotated data is required and a common protocol must be adopted to facilitate the merging of different repositories. In this context, the Fetal Tissue Annotation and Segmentation Challenge (FeTA), which was part of the International Conference on Medical Image Computing and Computer-Assisted Intervention (MICCAI) in 2021 and 2022, makes an important effort to define a common annotation protocol among different centers and build a freely available dataset of annotated fetal images that can be used for training and testing automated multiclass image segmentation algorithms.

The method proposed by Khalili et al. (2019) [30] is the only one developed to directly annotate acquired coronal images, thus minimizing image pre-processing. It consists of two consecutive blocks composed of identical 2D U-Net architectures [8]. The first block extracts the brain from the acquired slice, whereas the second block annotates the brain into seven tissue classes: cerebellum (CB), basal ganglia and thalami (BGT), ventricular cerebrospinal fluid (vCSF), WM, brain stem (BS), cGM, and extracerebral cerebrospinal fluid (eCSF). Subsequently, segmentation refinement is performed by removing small isolated clusters of voxels outside the intracranial. The networks are trained by randomly adding synthetic inhomogeneous intensity data to address the inhomogeneous intensity artifacts.

In 2020, Payette et al. [68] applied the U-Net architecture [8] to segment axially oriented fetal images into seven tissues: CB, GM, deep gray matter (dGM), eCSF, lateral ventricles (LV), and BS. They used a transfer learning training strategy to evaluate the performance of the proposed network with different high-resolution reconstruction methods. The network is originally trained on data obtained via MIALSRTK [23] and subsequently retrained with a transfer learning strategy on data reconstructed using different tools, such as SVRTK [24] and NiftyMIC [22]. The labels are manually annotated, except for the SVRTK and NiftyMIC reconstructions, which are derived by the rigid registration on the corresponding MIALSRTK images.

A different approach is presented by Payette et al. (2021) [37], who reported the results of the FeTA Challenge 2020. The study included ten algorithms, proposed by four different research groups for the challenge. The algorithms are validated on a common dataset of images previously pre-processed and segmented according to a seven-tissue protocol previously introduced in [68]. DL-based algorithms can be grouped according to their underlying architectures:

- KispiU: U-Net-based [8] method proposed in four variants. Three independent 2D U-Net architectures are trained on different orientations images (axial, sagittal, and coronal), and a 3D U-Net is proposed as a comparison method.
- Segmenting Brain Regions (SeBRe): a toolbox based on high-throughput mask R-CNN [112]. It is constructed using a convolutional backbone comprising the first five stages of the very deep ResNet101 [102] and feature pyramid networks (FPNs) [113]. The input feature map is processed by a CNN through a region proposal network (RPN) in a sliding-window fashion, and the predicted n ROI are forwarded from each window to the mask R-CNN. The mask R-CNN is based on a multi-headed FPNs: the "classifier" acts as an identifier, the "regressor" detects the brain region and computes region-specific bounding boxes, and the "segmenter" predicts the masks using a FCN [85].
- IBBM: custom implementation of 2D U-Net [114] proposed in three variants, each trained on images with a precise orthogonal orientation (similar to KispiU). In contrast to the original U-Net implementation [8], the encoder is composed of a ResNet [115] backbone that is pre-trained on the ImageNet dataset [116]. Furthermore, another variant is proposed based on the weighted merging strategy of the aforementioned 2D U-Net outputs.

In 2021, the FeTA Challenge was held at MICCAI 2021. Payette et al. (2023) [73] described the results of the challenge. A total of 21 algorithms were submitted, and the challenge results showed that almost all algorithms performed similarly. Among the top five ranking teams, all used 3D U-Net. For a more detailed description of the proposed algorithms, please refer to the original manuscript. Although a successive edition of the FeTA Challenge was held at MICCAI 2022, a corresponding article has not yet been published.

In their study, Fidon et al. (2021) [69] aimed to train a DL model with partially segmented images, thereby handling the presence of missing labels in the training set using a specific formulation of the loss function called Leaf-Dice loss [94,97]. With Leaf-Dice loss, they trained a 3D U-Net backbone architecture [86] to segment fetal brain images into eight tissues: WM, LV, CB, eCSF, cGM, dGM, BS, and corpus callosum (CC).

Zhao L. et al. (2022) [70] exploited the 3D nature of brain tissues and proposed a 3D extension of the original 2D U-Net [8] to directly annotate the whole-brain volume. The proposed method is compared with a 4D atlas-based [117] label propagation method on a segmentation task of six tissues (cGM, dGM, WM, CSF, CB, and BS) in both healthy subjects and patients with a congenital heart disease diagnosis.

Karimi et al. (2023) [71] introduced a novel training approach of the nnU-Net (i.e., 3D U-Net) [9] to segment fetal brain tissue from artificial "noisy" annotations, which are derived through a semi-automatic procedure based on multi-atlas segmentation (i.e., deformable registration with probabilistic atlas fusion), followed by manual correction of large errors. The strength of their training approach lies in a label-smoothing procedure coupled with a loss function that properly accounts for the uncertainty in tissue boundaries. The adopted loss function is a combination of loss functions based on the cross-entropy loss, which treats certain and uncertain regions differently. Using the proposed approach, a fetal brain is segmented into >30 relevant tissue compartments, leading to a substantial reduction in annotation time.

Huang et al. (2023) [72] designed a lightweight fetal brain tissue segmentation model that integrates a CNN-based encoder-decoder architecture with a transformer-style module called the contextual transformer (CoT) block. The CoT block integrates both contextual information mining and self-attention learning into a unified architecture [118] to guide the learning of a dynamic attention matrix, thereby strengthening the capacity of image feature representation. In addition, a hybrid dilated convolution module is introduced in the last layer of the decoder to effectively extract global contextual information from the fetal brain. The proposed approach segments the fetal brain according to the seven-tissue protocol introduced in [68].

3.4. Miscellaneous applications: brain extraction or structure segmentation as part of a processing pipeline

In this section, we report some studies that present a fetal brain segmentation step, not as the main aim of the proposed method but as part of a broader pipeline.

In 2018 and 2020, Ebner et al. [22,74] introduced a toolkit for the automated isotropic reconstruction of the fetal brain from multiple 2D fetal scans. The toolkit consists of a two-stage CNN-based method for brain extraction followed by a single-parameter, outlier-robust, super-resolution reconstruction algorithm, as well as a high-resolution alignment algorithm in a standard anatomical space. Therefore, the brain extraction method can be directly applied to the acquired data, independent of subsequent reconstruction steps. In particular, it first localizes the fetal brain with a "coarse segmentation" stage, then extracts the brain with a "fine segmentation" stage. Both segmentation stages adopt a 2D P-Net [42] structure as the backbone. However, a multiscale loss function is introduced in the fine segmentation step, allowing for noise

and spatial inconsistency reduction in the prediction of fetal brain segmentation.

Li H. et al. (2021) [75] proposed an automated pipeline for brain extraction, super-resolution reconstruction, and 4D brain atlasing to quantitatively map in utero fetal brain development from a Chinese cohort of 23–36 GAs. The brain extraction task is performed using three U-Nets, one for each orthogonal orientation (axial, coronal, and sagittal) based on the original U-Net implementation [8].

Avisdris et al. (2021) [76] developed a DL-based method to compute fetal brain linear measurements from MR images, such as the cerebral biparietal diameter, bone biparietal diameter, and trans-cerebellum diameter. Their approach, which follows the same rationale used in manual measurements, consists of five stages: (1) fetal brain ROI detection via an anisotropic 3D U-Net classifier, (2) selection of the coronal slice used as a reference via a CNN, (3) slice-wise segmentation of fetal brain structures via a multi-class U-Net classifier, (4) computation of the fetal brain mid-sagittal line and fetal brain orientation via a support vector machine algorithm, and (5) computation of fetal brain measurements. To perform the fetal brain structure segmentation stage, they adopted a 2D U-Net [8], consisting of a ResNet34 [102] encoder pre-trained on the ImageNet dataset [116].

4. Discussion

Fetal brain segmentation from MR images is hindered by several challenges related to the intrinsic segmentation task and the fetal scenario. The main criticalities are reduced brain size and motion artifacts, despite the adoption of fast 2D sequences instead of the high-quality 3D sequences usually performed on adults. Another issue is the public availability of only narrow datasets for the development of automatic segmentation methods. Different approaches based on unsupervised classification, atlas fusion, deformation, and parametric methods were presented in the review by Makropoulos et al. (2018) [13]. Recently, the availability of high-performance GPUs and new datasets has led to the proliferation of DL-based methods in the fetal imaging context. These advanced methods have engendered significant segmentation improvements and made DL the best approach in the field, as reported in the recent FeTA Challenge [73], where all the proposed methods are DL-based.

In this scenario, several challenges should be considered when addressing fetal brain segmentation. The first is the presence of extra tissue (e.g., placenta and amniotic sac) in addition to the fetal brain in the acquired images. Thus, a localization step should be performed to detect the fetus (or fetuses in a twin pregnancy scenario) and its brain, discerning it from the mother's structures. Consequently, most of the brain extraction methods presented in the Results section are part of a more complex analysis pipeline [22,119] that includes preliminary operations, such as brain localization and ROI cropping. Second, fetal movements cannot be restrict during acquisition. Fast 2D sequences are more commonly used than 3D sequences owing to their minor susceptibility to fetal movement. Anyway, fetal movements cannot always be overcome with these sequences, and may result in a stack of slices that do not capture adjacent portions of the fetal brain. Nevertheless, in 21 of the 26 studies presented in the Results section, 2D segmentation algorithms are generally preferred to 3D algorithms for the extraction of the fetal brain even if they present some disadvantages (e.g., the anisotropic voxel size, the inability to exploit the tridimensional nature of the fetal brain or to uniformly segment the whole fetal brain). Super-resolution reconstruction algorithms overcome these problems, thereby supporting a 3D approach to segmentation tasks. Unfortunately, reconstruction algorithms require preliminary steps that have not yet been standardized, further complicating the development of segmentation algorithms based on their outputs. Third, the majority of brain segmentation methods presented in this review adopt publicly available datasets originating from multicenter collaboration to ensure a sample size adequate for the training of DL methods. These databases, usually composed of fast T2w spin-echo sequences, are small and not standardized, as each center presents ad hoc MRI acquisition parameters (e.g., in-plane resolution, slice thickness, slice gap, echo time, and repetition time). Consequently, the DL algorithm can benefit from this data heterogeneity, reducing the risk of overfitting and improving the generalization of the problem, even if this may result in slightly less accurate segmentation. Therefore, some of the presented methods include post-processing steps such as refinement algorithms (e.g., connected-component labeling in [45,48,50,52]) or even merging strategy techniques [37,54,55] to achieve the finest segmentations. Finally, the complicated nature of the fetal brain with the rapidly changing contrast among structures/tissues and the substantial shape variation of the brain as growth proceeds, could lead to erroneous segmentation. Segmenting a fetal brain in the third trimester (i.e., $>$ 28 gestational weeks) or in the early diagnostic stages (i.e., $<$ 22 gestational weeks) of the pregnancy is different owing to the ongoing neuronal migration and structure formation (e.g., sulcal/giry pattern). Therefore, a brain segmentation approach that can account for the fetal GA would result in more precise characterization of the fetal brain structures [1,2]. Despite the importance of the topic, only four studies have explicitly evaluated the segmentation performance in different pregnancy stages [59,60,71,72]. Meanwhile, all the other methods included samples collected in a wide range of GAs, spanning from 20 to 40 weeks, without investigating the correlation between algorithm performance and fetal GAs. Moreover, pathologies that alter the normal brain morphology may occur during pregnancy and affect segmentation performance. Hence, training a segmentation algorithm exclusively with healthy samples can only reduce its robustness because an altered morphology may not be correctly described by the priors implicitly learned in the training phase. Only a few studies have explicitly considered the presence of pathologies such as spina bifida [22,37,54,55,62,67,72–74]. This may be due to the small sample size in the early stages of pregnancy and in pathological cases. In this regard, international collaboration on projects such as the Human Connectome Project (dHCP[4]) and challenges such as the recent FeTA Challenge[5] are crucial for method development on challenging topics.

Common applications were identified in the reviewed studies. Most of the presented methods adopt a CNN, particularly a U-Net, as the backbone architecture. The U-Net architecture and its related developments, such as nnU-Net, are deep learning benchmarks for biomedical image analysis and use in other fields [120,121]. This encourages the adoption of solutions developed in different contexts (e.g., on different populations such as adults or different imaging modalities such as ultrasound) and training techniques that can overcome the lack of large fetal MRI datasets (e.g., transfer learning). Recently, reconstruction algorithms have been increasingly adopted by the scientific community to generate high-resolution fetal brain volumes (e.g., preprocessing pipeline of the FeTA Challenges). In this scenario, 3D segmentation approaches are gaining popularity because of their ability to exploit the intrinsic relationship between adjacent voxels and reduce the partial volume effect at structural boundaries. However, in this context, the segmentation performance depends strictly on the quality of the reconstructed images, tying the two methods together. One possible solution is to train the segmentation network with volumes reconstructed using multiple techniques to reduce the impact of a single preprocessing pipeline [37,73].

Interest in fetal brain segmentation continues to increase as emerging and innovative technologies empower the acquisition of multiple and better-quality images, which can allow quantitative evaluation of the brain. Accordingly, several research groups have adopted open-source policies for their segmentation software, thus promoting collaboration with other centers to further develop their solutions.

[4] http://www.developingconnectome.org/
[5] https://feta.grand-challenge.org/

Possible future directions in this field include the development of segmentation algorithms that can characterize potential biomarkers and support early detection of specific clinical conditions. Furthermore, multimodal MRI acquisition (i.e., diffusion tensor imaging and functional MRI) would enable the adoption of a multichannel MRI embedding strategy, which would consequently surmount the segmentation accuracy plateau currently occurring in single-channel approaches.

5. Conclusion

Segmentation of the fetal brain is gaining increasing attention owing to the contribution of better-quality images and strong interest in fetal development to aid in the detection and characterization of fetal pathologies. In this review, we surveyed the existing techniques described in the literature concerning fetal brain segmentation from MRI using DL methods and highlighted many crucial issues for future research in the field. We classified the segmentation techniques according to their main aims: brain extraction, main brain structure segmentation, and labeling of several brain tissues. We identified some commonalities among different research groups, suggesting a convergence of the adopted solutions, which is also supported by their similarly reported findings. The development of novel methods and approaches that are adequately robust to address the rapidly changing morphology of fetal brains across gestational ages could lead to the detailed characterization of pathological cases for translation into clinical practice.

CRediT authorship contribution statement

Tommaso Ciceri: Conceptualization, Resources, Writing – original draft, Writing – review & editing. **Letizia Squarcina:** Supervision, Writing – review & editing, Funding acquisition. **Alice Giubergia:** Writing – review & editing. **Alessandra Bertoldo:** Supervision, Writing – review & editing. **Paolo Brambilla:** Writing – review & editing, Funding acquisition, Project administration. **Denis Peruzzo:** Supervision, Conceptualization, Writing – review & editing, Funding acquisition.

Declaration of competing interest

The authors declare no competing interests.

Data availability

This review article does not include the use of original data and code. For further information regarding the data and code from studies cited within, please refer to the original article.

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Appendix A. Supplementary data

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