Automatic Detection of Papilledema through Fundus Retinal Images using Deep Learning

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Abstract: Papilledema is a syndrome of the retina in which retinal optic nerve is inflated by elevation of intracranial pressure. The papilledema abnormalities such as retinal nerve fiber layer (RNFL) opacification may lead to blindness. These abnormalities could be seen through capturing of retinal images by means of fundus camera. This paper presents a deep learning-based automated system that detects and grades the papilledema through U-Net and Dense-Net architectures. The proposed approach has two main stages. First, optic disc and its surrounding area in fundus retinal image are localized and cropped for input to Dense-Net which classifies the optic disc as papilledema or normal. Second, consists of preprocessing of Dense-Net classified papilledema fundus image by Gabor filter. The preprocessed papilledema image is input to U-Net to achieve the segmented vascular network from which the Vessel Discontinuity Index (VDI) and Vessel Discontinuity Index to disc proximity (VDIP) are calculated for grading of papilledema. The VDI and VDIP are standard parameter to check the severity and grading of papilledema. The proposed system is evaluated on 60 papilledema and 40 normal fundus images taken from STARE dataset. The experimental results for classification of papilledema through Dense-Net are much better in terms of sensitivity 98.63%, specificity 97.83%, accuracy 99.17%. Similarly, the grading results for mild and severe papilledema classification through U-Net are also much better in terms of sensitivity 99.82%, specificity 98.65%, and accuracy 99.89%. The deep learning-based automated detection and grading of papilledema for clinical purposes is first effort in state of art.

Keywords: Optic Nerve; U-Net; Dense-Net; Mild Papilledema; Severe Papilledema; Healthcare.

1. INTRODUCTION

Currently deep learning emerged to be highly assisted in cancer diagnosis issues from medical images analysis and classification such as brain tumor (Iqbal et al., 2018; Saba et al., 2020; Amin et al., 2019), skin cancer (Khan et al., 2019), breast cancer (Mughal et al., 2018a,b; Mughal et al., 2017; Sadad et al., 2018), retina diseases (Jamal et al., 2017), lungs cancer (Khan et al., 2019) and so forth. The retina is most significant part of human's eye in vision process. Papilledema (swelling of retinal optic disc) is a disease caused by consistent high intracranial pressure (ICP), which happened due to elevated cerebrospinal fluid (CSF) in the brain and optic nerve (behind optic disc) (Tannenbaum & Mandelcorn, 1990). The various imaging instruments can be used to capture the retinal images for papilledema and other retinal diseases such as fundoscopy and optical coherence tomography (OCT). The schematic diagram (examination, 2021) shows the fundus examination for normal and papilledema retina in figure 1.

Rapid advancements in ophthalmology also raised the need for computer-aided classification systems for a variety of cancer and ocular diseases (Husham et al, 2017; Fahad et al., 2018; Saba, 2020). Papilledema is an ocular condition in which the eye's optic disc swells due to increased ICP. It begins with headaches, nausea and blurred vision. If left unchecked, it can result in irreversible vision loss and, in some circumstances, death. Papilledema happens due to an increase in ICP caused by high blood pressure or hypertension. Any patient who develops papilledema due to hypertension indicates malignant hypertension and must be treated as an emergency (Akbar, Akram, Sharif, Tariq, Khan, 2018; Akbar, Hassan, Akram, Yasin, Basit). Papilledema is not exclusively affected by hypertension; a variety

of other factors could also cause it. In fact, papilledema is not a disease rather a symptom of many other disorders (Kannatey-Asibu Jr, 2009). If papilledema is noticed in a patient, the basic cause should be determined promptly. Advanced stages of papilledema can signify severe disease progression to brain tumor or brain hemorrhage. As a result, papilledema can be identified early enough for better cure (Kannatey-Asibu Jr, 2009). On a fundus image, various symptoms of papilledema including blurring of the optic disc (OD) border, the presence of a circumferential ring across the OD and blood vessel dilation are happened (Kannatey-Asibu Jr, 2009). The normal optic disc and swelled optic disc (Akram et al., 2020) are shown in Figure 2.

Papilledema initially occurs on optic nerve head (ONH), progresses outside the boundary of ONH at severe stages and damages the ONH. The optic nerve with central retinal vein and artery originates from ONH and goes to brain for vision (Chappelow & Traboulsi, 2011). The optic nerve fibers also called axons which are made of ganglion cells and nearly 01 million axons originates from optic nerve and Elchaig's ring around ONH is well-defined nearby Bruch's membrane (Jonas, Budde, & Panda-Jonas, 1999). Hence severe damage of optic nerve may cause various ONH diseases including papilledema (Cameron, 1933; Riordan-Eva, 2004). The raised ICP is vision-threatening (Cameron, 1933), although it has no apparent abnormalities except increased CSF (Chagot et al., 2017; Corbett & Mehta, 1983). The swelling of axons and ONH's peripapillary area is responsible for retinal blood vessels obscuration and elevated ICP responsible for papilledema. The various abnormalities such as cotton wool spots, hemorrhages, exudate, Idiopathic Intracranial Hypertension (IIH), arteriovenous fistulae, and papilledema have occurred due to increased ICP (Asghar, Khan, & Asghar, 2009). Generally, IIH also called pseudotumor cerebri creates papilledema with temporary visual obscurations, vomiting and headache in over weighted females and children (Sahin, Cingü, Ari, Çinar, & Çaça, 2012). The distinction of pseudo papilledema (ONH elevation) and papilledema is difficult at early stage of optic disc swelling (Atta, 1988). Still, clinical tests like computed tomography (CT) and magnetic resonance imaging (MRI) may differentiate the papilledema from pseudo papilledema. So, timely papilledema detection is vital for patient's recovery. The papilledema is graded into five stages with 0 stage (normal) (Frisén, 1982) as shown in Table 1.

Additionally, this paper has further four major sections. Section 2 explores the related studies on papilledema identification. Section 3 deals with feature extraction, training, testing using deep learning using benchmark dataset. Section 4 exhibits experimental details and results. Finally, Section 5 concludes research with future directions.

2. RELATED WORK

While several studies have been conducted to diagnose papilledema using OCT, still this area is fresh for further research to detect and rate papilledema using fundus images through computer aided diagnosis. OCT is a safer method for diagnosing multiple retinal disorders including papilledema than fundoscopy (Driessen et al., 2014). The thickness of the RNFL, volume and elevation of the ONH, total retinal thickness (TRT), and macular thickness can all be calculated in the retinal OCT image. OCT image (Cat Nguyen Burkat, 2021) of the ONH exhibited in Figure 3.
Various efforts have been performed to observe papilledema in various groups of individuals, which are discussed here. Varma et al. (Varma, Bazzaz, & Lai, 2003) in Latin America studied the retinas of adults and discovered that macular thickness and peripapillary RNFL decline with age instead of gender. Gabriele et al. (Gabriele et al., 2007) identified the thickness of RNFL at diverse positions on the stable retina of patients and the researchers (Varma et al., 2003) examined retinas of adults in Latin America and discovered that rather than gender, macular thickness and peripapillary RNFL decrease with age. Similarly, Turk et al., (2012) conducted research on children ranging in age from six to sixteen years old. Macular volume and thickness and peripapillary RNFL were found to be unrelated to axial length or spherical equivalence and age. Another research (Leung, Huang, Lam, 2010) looked at Hong Kong children aged six to seventeen. It was discovered that the OCT dimensions, axial length, and RNFL thickness were unaffected by age. A survey of children aged five to fifteen years old was conducted in North America (Yanni et al., 2013). It was discovered that the thickness of the RNFL is unrelated to age for a significant pediatric population. Implicitly, the study recorded a 95 percent accuracy for getting good OCT images of kids aged five and up, while the researchers (El-Dairi, Asrani, Enyedi, & Freedman, 2009) found that OCT dimensions varied by age, race and axial length. They practiced 286 balanced retinal images taken from children aged three to seventeen.

The above studies don't assess standard OCT values for children under the age of three, which is an ongoing concern, but another analysis (Prakalapakorn et al., 2012) found that criteria of OCT don't alter significantly in stable kids up to the age of four and they suggested the OCT, rather than generic normative results, could be used to track the retina of children over time.

Several studies have clarified the dynamic association between OCT parameters, ICP, and papilledema. For example, the relationship between OCT and papilledema grading on the Frisen scale is clarified (Nguyen, Balmitgere, Bernard,

Tilikete, & Vighetto, 2012; Scott, Kardon, Lee, Frisén, & Wall, 2010). Nguyen, A. M., et al. (Nguyen et al., 2012) observed the TRT and RNFL thickness and discovered that TRT is much sensitive measure to detect moderate papilledema. In 36 patients with papilledema, a study (Ahuja, Anand, Dutta, Kumar, & Kar, 2015) found a strong correlation among RNFL thickness of R = 0.79 and Frisen scale grading, while the researchers (Scott et al., 2010) found that RNFL thickness as well TRT were associated with Frisen grade of R = 0.87 and R = 0.85, respectively and also discovered that the shift in TRT is directly proportional to the severity of papilledema and TRT may be a satisfactory parameter for studying extreme papilledema. A few studies have also shown a connection between ICP and OCT. The authors (Kaufhold et al., 2012) determined that optic nerve head volume (ONHV) is a good parameter for ICP than RNFL thickness. The study's flaw was that it measured ICP from LP (Lumbar Puncture) opening stresses, which could occur somewhere between zero and 24 months after the OCT examination. In few instances, there is a significant time difference between OCT and ICP measurements. According to the findings of these experiments, TRT, RNFL thickness and ONHV are linked to LP opening pressure calculation and Frisen scale grading. Another research (Skau, Milea, Sander, Wegener, & Jensen, 2011) compared papilledema and OCT in 20 patients, finding that increased ICP through pressure of LP opening observed by direct fundoscopy was 80.0 percent and 70.0 percent through fundus images, respectively. Peripapillary average retinal thickness was detected 90% of the time in an OCT scan, and peripapillary RNFL thickness was detected 85.0 percent of the time. Finally, OCT parameters, rather than fundoscopy, are a more accurate predictor of increased ICP.

There is no major research on automatic papilledema identification using fundus images. KN Fatima, et al. (Fatima, Akram, & Bazaz) proposed a pre-programmed system to detect papilledema through color fundus images. For this purpose, authors took 30 fundus images of Papilledema patients from the STARE database. Images as mentioned earlier, were tested through pre-processing and feature extraction phases. In classification, 2-fold cross-validation was employed on the retinal dataset. Authors attained 100% sensitivity, 95% specificity, 91.67% precision and 96.67% accuracy. The results show that the combination between extracted features and SVM combination came out with promising differentiation between papilledema-free fundus images and papilledema fundus images. Yousaf, Kamran, et al. (2016) (Yousaf, Akram, Ali, & Sheikh) proposed a robust technique to overcome Papilledema disease using a supervised SVM-RBF classifier. This computer-based automated system for detection and observance will help the clinicians detect the papilledema accurately. The authors used 46 colored fundus images dataset for testing and training the classifier. After the preprocessing and feature extraction phases, the authors achieved an accuracy of 95.65%. The proposed framework outperformed previously proposed automated processes. They demonstrated that the proposed ML system could be efficiently implemented in automatic detection of papilledema (Saba et al., 2018). Fatima, et al. (Fatima, Hassan, Akram, Akhtar, & Butt, 2017) detected Papilledema disease using a supervised SVM classifier. Incorporating STARE dataset repository and local dataset, they gathered 160 colored retinal fundus images to test the proposed method. These scans were categorized into 4 groups based on different properties: color, texture, vascular and disc margin obscuration features. After that preprocessing, extracting the features and classification, the authors achieved an accuracy of 85.9% for combined test set. This ultra-modern system will help physicians to diagnose the patients with more accurate results. However, the authors proposed system has a limitation that includes the poor quality of fundus scans, leading them to incorrect classification.

Akbar et al. (Akbar, Akram, Sharif, Tariq, & ullah Yasin, 2017) proposed an automatic method that detects papilledema in fundus retinal images. In the proposed method, 23 features were selected for classification of papilledema affected images. The classifier SVM along with RBF kernel was used in classification phase. The dataset consists of 160 fundus retinal images from STARE and local dataset. The results showed that the proposed method achieved 92.86% accuracy for papilledema classification and 97.85% accuracy for mild and severe papilledema classification on local dataset. Akbar et al. (Akbar, Akram, Sharif, Tariq, & ullah Yasin, 2018) proposed a method that was consisted of two parts; i.e. computation of arteriovenous ratio and analysis of ONH area to detect papilledema. The first part used hybrid features in classification with SVM-RBF classifier and the second part performed ONH region analysis for papilledema signs. In the proposed methodology the datasets (VICAVR, INSPIRE-AVR, local dataset) were used in the first module, and STARE and local dataset were used in the second part of the proposed methodology. The results thus obtained exhibited that the proposed method of the first module attained 95.10%, 95.64%, and 98.09% accuracies and the second module attained 95.93% and 97.50% accuracies, respectively. Milea, Dan, et al. (Milea et al., 2020) proposed an analytical technique using a Deep Learning classifier (U-Net) to detect papilledema. The authors used local fundus photographs from multiple populations. The proposed system consists of the following methods: 1) Study design and oversight 2) Image acquisition 3) Study patients 4) Definition of optic-disk abnormalities 5) Development of Deep-Learning classification model 6) Statistical analysis. After conducting all over the experiments and calculations they concluded the results with 96.4% sensitivity and

84.7% specificity. Nevertheless, it still has some limitations including an imbalance in class distribution among groups and labeling errors.

To conclude so far researches, main focus was on OCT's ONH volume but not on fundus features. Accordingly, the main contribution of proposed approach are as follows:

- A fully automated deep learning-based system is proposed to detect and grade papilledema through fundus retinal images using deep learning models first time in state of the art.
- The proposed system detects and grades papilledema at early and severe stages. This fully automated system could be implemented in clinics to support the ophthalmologist in reliable decision making.

3. PROPOSED METHODOLOGY

In this article, a deep learning-based automated method for detecting papilledema is proposed. The proposed system composed of two main phases: OD extraction image and classification of OD extracted image by Dense-Net (Huang, Liu, Van Der Maaten, Weinberger, 2017) and retinal blood vessels segmentation of papilledema image through U-Net (Ronneberger, Fischer, & Brox) for calculation of Vessel Discontinuity Index (VDI) and Vessel Discontinuity Index to disc proximity (VDIP). The mild and sever papilledema are based on VDI and VDIP values. Figure 4 depicts the proposed system's architecture.

3.1 Preprocessing and Optic Disc Extraction

Papilledema is a condition that affects the anatomy of OD and development of blood vessels in the disc's vicinity. An automatic device for papilledema can examine the OD and its neighboring blood vessels as well as the texture, color, and degree of disc obscuration. The proposed system removes the optic disc during the preprocessing period to facilitate the development of a fully automated device. Since the OD is the bright yellow spherical part of fundus image and its form and features may be affected by various retinal diseases. The proposed method makes use of Usman et al.(Usman, Khitran, Akram, Nadeem) robust optic disc localization method. Finally, a disc segmentation algorithm is used to detect the boundary of the object. (Salam, Khalil, Akram, Jameel, & Basit, 2016), as shown in figure 4 of the proposed model.

3.2 Classification of Papilledema

Dense-Net has performed the classification of papilledema OD images and normal OD images. Dense-Net falls in the category of classic networks. Figure. 2 shows the architecture of dense blocks with five layers. By using the composite function operation, previous layer's output serves as an input to the second layer. This multi-layer operation consists of four layers: convolution, pooling, batch normalization, and non-linear activation. Dense-Net is a form of convolutional neural network that makes use of dense connections between layers through Dense Blocks. Both layers of the same feature-map size are linked together directly. To maintain the feed-forward nature, each layer receives additional inputs from preceding layers and transmits its own feature maps to subsequent layers.

Dense-Net is distinguished from other Convolutional Neural Networks by the fact that each unit within a dense block is bound to every other unit preceding it. To conclude, within a given block, the nth unit receives as input the feature-maps learned by the n-1, n-2, and so on down pipeline to first unit. Consequently, Dense-Nets could be implemented with a small number of parameters due to high degree of function sharing between the modules.

3.3 Retinal blood vessels Extraction

The detection of some retinal diseases as well as papilledema depends upon by analyzing of blood vessels in retina (Akbar et el., 2019), therefore, blood vessels are extracted for diagnosis and grading of papilledema from retinal images. For extraction of blood vessels from retinal images, U-Net deep convolutional neural network has been employed. Due to its successful, efficient, fast, and simple architecture, it swiftly progressed to a frequently used network in the domain of semantic segmentation of biomedical images. In this architecture, the preliminary series of convolutional layers are intermingled by making the use of max-pooling layers. These layers help in decreasing the size of the input image sequentially. The other series of convolutional layers are interspersed with up-sampling layers, which sequentially increases the size of the input image. Before each layer of the ReLu activation function, a batch normalization layer is placed. Figure 1 demonstrates U shape network architecture of U-Net Deep Convolutional Neural Network. The U-Net architecture is encoder-decoder in nature, with the decoder eventually recovering it. As a consequence, rather than classifying an input image, it generates a pixel-by-pixel probability map. Furthermore, it does not necessitate a large number of training samples and can be trained successfully with just a few images. Gabor filter is applied on each image in the preprocessing step before feeding to U-Net architecture.

3.4 Grading of Papilledema

The covered veins and surrounding blood vessels of ONH are engorged and obscured by edematous RNFL as a result of papilledema. The distorted boundaries and covered vessels in the peripapillary region create whitish OD. Swelling of OD is associated with obscuration of OD's arteries and encircled nerve fibers. Segmented blood vessels are used to find and measure obscured retinal vessels on OD and peripapillary areas.

Vessel Discontinuity Index (VDI): It measures the degree of discontinuity of vessels in a vascular area. The vascular image in normal retina includes connected vessel regions, while the papilledema image consists of much disconnected vessel regions. The number of disconnected vessel regions of vascular image is referred to as Vessel Discontinuity Index (VDI) and it is measured as seen in figure 5. The number of vascular regions is calculated using connected component marking with 8-connectivity in binary vascular image.

Vessel Discontinuity Index to disc proximity (VDIP): Because of vessel obscuration, ONH and peripapillary area are most affected. The ONH proximity area is cropped to decide the VDIP and it could be measured as seen in figure 5.

These regions make up the VDI total, whereas VDIP counts these vascular areas in region of interest (ROI) comprising only the OD. The approach counts the number of vascular areas as well as counts number of pixels in each area to compute the entire affected area. Figure 6 and 7 depict VDI and VDIP for a normal image and papilledema image.

4. EXPERIMENTS AND RESULTS

4.1 Dataset: Benchmark datasets play an important role in experiments, results authentications and comparisons (Rad et al., 2016; Rehman et al., 2018). The images used are taken from Structured Analysis of the Retina project also known as STARE dataset (Hoover & Goldbaum, 2003) benchmark dataset composed of around 400 fundus images and 100 images are used to authenticate network performance. The 60 images without swelling of OD show no signs of papilledema while 40 images having papilledema signs. The resolution of these images is 700x605 pixels. Subsequently, manual augmentation, total number of images become 500 hundred, out of which 120 have been used for validation.

4.2 Training of Dense-Net: In a Dense-Net architecture, each layer is connected to every other layer, hence the named as Densely Connected Convolutional Network. The feature maps of all previous layers are used as inputs for each layer, and each subsequent layer's feature maps are used as inputs. This is as simple as it may sound; Dense-Nets essentially connect every layer to every other layer. This is the main idea that is extremely powerful. The input of a layer inside Dense-Net is the concatenation of feature maps from previous layers.

To validate the classification system's performance for fundus images of STARE dataset into normal and papilledema, Prior to feeding the fundus images to dense-net, images have been cropped from the fundus OD area which provides most useful information about papilledema. In dense-net, 256x256 dimensions are taken for input images. The augmentation process is performed to increase the number of training images. The 70% of preprocessed fundus images were used to train the network and 30% were used for validation. The starting learning rate was $1x10^{-4}$ and number of iterations was 700. The dense-net classification precision and loss curve with each iteration has been shown in figure 8. The Figure 10 shows the confusion matrix for dense-Net. According to this, the network has incorrectly classified only one image.

4.3 Training of U-Net: The U-Net is a semantic segmentation architecture. It has two paths: one that contracts and one that expands. The convolutional network's contracting direction resembles the traditional architecture. It consists of two 3x3 convolutions that are applied multiple times. A rectified linear unit (ReLU) and a down-sampling 2x2 max pooling operation with stride 2 are included with each. For each down sampling process, we double the number of feature channels. A concatenation with the contracting path's correspondingly cropped feature map, a 2x2 convolution that halves the number of feature channels, and an up sampling of the feature map and two 3x3 convolutions, each preceded by a ReLU, make up each step of the expansive path. Cropping is important since each convolution results in the loss of boundary pixels. A 1x1 convolution is employed in last layer to assign each 64-component function vector to the desired number of groups. The network has a total of 23 convolutional layers.

The proposed U-Net based network for extraction of blood vessels has been trained using patches of a size 32x32 pixel. These patches were obtained from images of STARE dataset. The patch scale of 32x32 resulted in the highest classification accuracy for pixels by CNN. Each patch was created randomly from the full image's core. Additionally, the patches that extend partly or completely beyond the Field of View (FOV) are selected. Accordingly, network

learns how to discriminate the FOV border from blood vessels. Training set composed of 70% of the dataset while 30% for validation, selected randomly. The training has been performed for 150 iterations, with a mini-batch size of 32 patches. Specifications of system include core i9, 10th generation with GPU RTX 2080 Ti (11 GB). The total training time was 6 hours and 37 minutes for both Dense-Net and U-Net. The classification precision as well as loss curve with each iteration have been shown in figure 9. Figure 10 shows the confusion matrix for U-Net.

4.4 Experimental Results: The statistical metric "Dice coefficient" has been used in evaluation of papilledema OD classification along with ground truths of 100 OD images in the dataset for validation of the proposed papilledema detection method as shown in equation (1).

$$Dice\ Cof. = \frac{2|A_{n/p} \cap B_{n/p}|}{|A_{n/p}| + |B_{n/p}|} \quad (1)$$

In equation (1), $A_{n/p}$ represents normal (n) OD image or papilledema (p) OD image after Dense-Net classification and $B_{n/p}$ represents ground truth normal (n) OD image or papilledema (p) OD image in annotated image of dataset.

Other than dice coefficient, True Positive (TP), True Negative (TN), False Negative (FN) and False Positive (FP) are used to calculate sensitivity, specificity & accuracy for evaluation of Papilledema classification performance with respect to ground truth OD images annotated images of dataset. Equation (2), (3) and (4) shows the formulas of sensitivity, specificity and accuracy, respectively.

$$SENSTY = \frac{TP}{[TP+FN]} \quad (2)$$

$$SPECTY = \frac{TN}{[TN+FP]} \quad (3)$$

$$\text{ACRCY} = \frac{[TP+TN]}{[TP+TN+FP+FN]} \quad (4)$$

The papilledema classification results by Dense-Net are illustrated in Table 2. It has been noticed that the Dense-Net shows remarkable results by achieving 99.17% accuracy, 97.83% specificity, 98.63% sensitivity. Table 3 depicts the proposed method results with state of methods and Table 4 depicts the classification results of mild and severe papilledema.

5. Conclusion and Future work

This article has presented an automatic method for detecting and grading papilledema. The presented technique outperformed previously published approaches in the state of the art. The cumulative findings in Table 3 reflect a higher degree of accuracy. To our understanding, one of the main achievements of this approach is the previously unrecognized grading of papilledema between moderate and serious. When doing annotations for the proposed scheme. Both symptoms of papilledema from MFS grades 1 and 2 are grouped together and considered it mild papilledema, while signs from grades 3 to 5 are grouped together and considered it severe papilledema stage. From 40 papilledema images, the ophthalmologists classified 11 images as mild and 29 as severe. As seen in Table 4, the suggested procedure produces significantly improved outcomes when scoring papilledema. The suggested procedure is extremely beneficial for ophthalmologists and patients in terms of automatically detecting papilledema and preventing vision loss. The proposed method could be effectively used in hospitals to diagnose moderate to serious papilledema. The same scheme may be expanded to provide more comprehensive disease classification. We need to build a huge dataset dedicated to papilledema in order for researchers to train and validate their deep learning algorithms in the future.

Highlights

The proposed system is a fully automated solution to detect papilledema at early and severe stages and it can be implemented in clinics to support the ophthalmologist in reliable decision making.

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Ethical Approval: In this presented research, experimentation is not performed on animals or humans; only benchmark publicly accessible dataset is used in experimentation.

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Figures and Tables titles