

Method for processing at least a pre-contrast image and a contrast image respectively depicting a body part prior to and after an injection of a first dose of contrast agent

5 FIELD OF THE INVENTION

The field of this invention is that of machine/deep learning.

More particularly, the invention relates to methods for processing at least a pre-contrast image and a contrast image respectively depicting a body
10 part prior to and after an injection of a first standard dose of contrast agent, in particular for generating a synthetic contrast image simulating said body part after an injection of a second dose of contrast agent which is higher than the standard dose.

15 BACKGROUND OF THE INVENTION

Contrast agents are substances used to increase the contrast of structures or fluids within the body in medical imaging.

They usually absorb or alter external radiations emitted by the medical
20 imaging device. In x-rays, contrast agents enhance the radiodensity in a target tissue or structure. In MRIs, contrast agents modify the relaxation times of nuclei within body tissues in order to alter the contrast in the image.

Contrast agents are commonly used to improve the visibility of lesions, notably in neuroimaging for the initial diagnosis and treatment planning of
25 brain tumors, such as glioma, brain metastasis, meningioma.

Dynamic susceptibility contrast (DSC) and Dynamic contrast enhanced (DCE), respectively leveraging T2 and T1 effects, are the two most common techniques for MRI. In both cases, a gadolinium-based contrast agent (GBCA) is injected intravenously to the patient and rapid repeated
30 imaging is performed in order to obtain a temporal sequence of images.

GBCA injection increases the sensitivity of MRI, allowing for instance the identification of smaller carcinogenic nodules, an earlier treatment

initiation and, in turn, improving patient survival and quality of life. One solution to further increase MRI sensitivity is to increase the injected quantity of GBCA.

However, based on precautionary considerations, recent clinical
5 guidelines suggest using the minimum dosage that achieves a sufficient contrast enhancement, and GBCA usage should therefore be as parsimonious as possible.

Three complementary research avenues for nevertheless improving MRI contrast and its lesion detection performance can be identified:

- 10 - Firstly, new contrast agents with improved chemical properties have the potential to improve the image contrast without increasing the injected dose of gadolinium. However, such agents are still under testing, and are likely to be even more expensive than GBCA.
- 15 - Secondly, novel MRI sequences, with or without contrast agent, may respectively replace or complement the routine contrast-enhanced T1 sequences. In particular, the turbo spin echo T1 sequence with variable flip angles (TSE) proved more sensitive than its gradient echo (GRE) counterpart and is now recommended
20 for brain tumor imaging, although some qualitative limitations were also identified in addition to the longer minimum scan time that may favor motion artifacts.
- 25 - Third, promising deep learning approaches are being increasingly proposed to automatically detect and delineate tumors, bearing the promise of uniform and constant accuracy levels with virtually instantaneous reading times. However, these deep learning algorithms are still under research and their performance remains insufficient for immediate large-scale deployment.

There is consequently still a need for a new method to further improve
30 sensitivity for contrast enhanced medical imaging.

SUMMARY OF THE INVENTION

For these purposes, the present invention provides a method for medical imaging, the method being characterized in that it comprises the
5 implementation, by a data processor of a second server, of steps of:

- (a) Obtaining (i) at least one candidate pre-contrast image and a candidate contrast image respectively depicting a body part prior to and after an injection of a first dose of contrast agent, wherein the first dose of contrast agent is higher than a low dose of contrast agent and the low dose is lower than a standard dose of contrast agent; and (ii) a convolutional neural network, CNN, being trained to reconstruct, from at least one pre-contrast input image and a low dose contrast input image respectively depicting the body part prior to and after an injection of the low dose of contrast agent, a standard dose contrast image depicting the body part after an injection of the standard dose of contrast agent;
10
15
(b) Generating a synthetic contrast image by applying the CNN to the at least one candidate pre-contrast image and the candidate contrast image.

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Preferred but non limiting features of the present invention are as it follows:

Said low dose is between 10 and 50% of the standard dose.

Said low dose is between 1/5 and 1/3 of the standard dose, preferably
25 around 25%

Said first dose is at least 50% of the standard dose.

Said first dose is at least 80% of the standard dose, preferably around 100% of the standard dose

So that said second dose is at least 240% of the standard dose,
30 preferably between 320% and 400% of the standard dose.

The at least one candidate pre-contrast image and the candidate contrast image are acquired by a medical imaging device connected to the second server, in particular an MRI scanner.

Said at least one pre-contrast candidate image includes a T1-weighted
5 pre-contrast image and the candidate contrast image is a T1-weighted image.

Said at least one pre-contrast image comprises three candidate pre-contrast images which includes the T1-weighted pre-contrast image, a T2-flair-weighted pre-contrast image and an ADC pre-contrast map.

The CNN is trained to reconstruct, from a T1-weighted pre-contrast
10 input image, a T2-flair-weighted pre-contrast input image, an ADC pre-contrast input map and a T1-weighted contrast input image respectively depicting a body part prior to and after an injection of said low dose of contrast agent, a T1-weighted low dose contrast image depicting said body part after an injection of said standard dose of contrast agent.

15 Step (b) comprising applying the CNN to the three candidate pre-contrast image and the candidate contrast image, so as to generate a synthetic T1-weighted contrast image.

Said CNN comprises an encoder branch followed by a decoder branch, with skip connections between the encoder branch and decoder branch.

20 The method comprises a previous step of training, by a data processor of a first server, said CNN from a base of sequences of at least one training pre-contrast image, a first training contrast image and a second training image respectively depicting a body part prior to, after an injection of said low dose of contrast agent, and after an injection of said standard dose of contrast
25 agent.

According to a second and a third aspect, the invention provides a computer program product comprising code instructions to execute a method for medical imaging according to the first aspect; and a computer-readable medium, on which is stored a computer program product comprising code
30 instructions for executing for medical imaging said method according to the first aspect.

BRIEF DESCRIPTION OF THE DRAWINGS

The above and other objects, features and advantages of this invention will be apparent in the following detailed description of an illustrative embodiment thereof, which is to be read in connection with the accompanying drawings wherein:

- figure 1 illustrates an example of architecture in which the method according to the invention is performed;
- figure 2 represents an example of training pipeline and operation pipeline of a CNN in the method according to the invention;
- figure 3 represents a preferred architecture of CNN used in the method according to the invention;
- figure 4 illustrates an embodiment of the method according to the invention;
- figure 5 compares T1c and T1c+ contrast images obtained using the method according to the invention.

DETAILED DESCRIPTION OF A PREFERRED EMBODIMENT

Architecture

The present invention proposes a method for medical imaging, in particular for processing by a convolutional neural network, CNN, at least a candidate pre-contrast image and a candidate contrast image respectively depicting a body part prior to and during or after an injection of a first dose of contrast agent.

By pre-contrast image, or "plain" image, it is meant an image depicting a given body part (to be monitored) prior to an injection of contrast agent, for a person or an animal. By contrast image it is meant an image depicting said body part during or after the injection of contrast agent.

In other words, if there is a temporal sequence of images, the first one is the pre-contrast image, and each of the following is a contrast image. Note that the contrast images may be images of a given phase (e.g. arterial, portal, delayed) or fully dynamic contrast enhanced (DCE).

5 In the following description, we will take the preferred example of brain imaging, i.e. said body part is the brain.

The (pre-contrast or contrast) images are either directly acquired, or derived from images directly acquired, by a medical imaging device of the scanner type.

10 Said imaging with injection of contrast agent may be:

- CT (Computed Tomography) → the medical imaging device is an X-ray rotational scanner capable of tomographic reconstruction;
- MRI (Magnetic Resonance Imaging) → the medical
15 imaging device is an MRI scanner;
- Mammography → the medical imaging device is an X-ray mammograph;
- Etc.

The acquisition of a said image may involve the injection of a contrast
20 agent such as gadolinium (GBCA) for MRI or appropriate x-ray contrast agents.

Note that the “images” can be 2D objects (with two spatial dimensions) but also possibly 3D objects (with three spatial dimensions), i.e. volumes constituted of stacks of bidimensional images as “slices” according to a third
25 spatial dimension - in other words, we have 2+1 spatial dimensions).

Furthermore, we can have a plurality of pre-contrast images and/or candidate contrast images.

In a preferred MRI embodiment, we have at least a T1-weighted pre-contrast image and a T1-weighted contrast image, in particular GRE (gradient
30 echo) T1-weighted pre-contrast/contrast images, but we may further have:

- a T2-flair-weighted pre-contrast image (in particular TSE (turbo spin echo)); and/or

- an ADC (apparent diffusion coefficient) pre-contrast map (automatically converted from EPI (echo-planar) DWI (diffusion weighted)),

Note that a TSE (turbo spin echo) T1-weighted contrast image can also
5 be available, but it will not be presently used.

The above-mentioned methods are implemented within an architecture such as illustrated in **Figure 1**, by means of a first and/or second server 1a, 1b. The first server 1a is the training server (implementing a training method
10 of the CNN) and the second server 1b is a processing server (implementing the processing method). It is fully possible that these two servers may be merged.

Each of these servers 1a, 1b is typically remote computer equipment connected to an extended network 2 such as the Internet for data exchange.
15 Each one comprises data processing means 11a, 11b of processor type (in particular the data processor 11a of the first server 1a have strong computing power, since learning is long and complex compared with ordinary use of the trained models), and optionally storage means 12a, 12b such as a computer memory e.g. a hard disk. The second server 1b may be connected to one or
20 more medical imaging devices 10 as client equipment, for providing images to be processed, and receiving back parameters.

Note that it is supposed that the imaging device 10 comprises an injector for performing the injection of contrast agent, said injector applying the injection parameters.

25 The memory 12a of the first server 1a stores a training database i.e. a set of images referred to as training images (as opposed to so-called inputted images that precisely are sought to be processed). Each image of the database could be pre-contrast or contrast, and contrast images may be labelled in terms of a dose of contrast agent injected. Note that images
30 corresponding the same injection (i.e. forming a temporal sequence) are associated into sequences.

Dose minimization CNN

In the following description, we will refer to a “low dose” and a “standard dose” of injected contrast agent. Both are predetermined. For convenience, a contrast image depicting a body part after an injection of the standard dose of contrast agent will be referred to as “standard dose contrast image”, and a contrast image depicting a body part after an injection of the low dose of contrast agent will be referred to as “low dose contrast image”.

The standard dose, or “full-dose”, is the recommended dose which is generally used for a medical examination. While side effects are possible, such dose is not particularly dangerous for the patient, and allows an image quality level sufficient for analysis/diagnostic purposes. In the case of GBCA, the standard dose is 0.1mmol/kg.

The low dose, or “reduced dose”, is a dose which is lower than the standard dose, and which causes less effects to the patient health. Said low dose may be any fraction of the standard dose and is preferably between 1/10 and 1/2 (between 10 and 50%) of the standard dose, preferably between 1/5 and 1/3 (between 20 and 33%) of the standard dose, preferably around 1/4 (25%). In the case of GBCA, the low dose is for instance 0.025mmol/kg (25% of 0.1mmol/kg).

Obviously, the low dose contrast image presents less contrast than the standard dose contrast image. And naively amplifying the contrast enhancement of a x% low-dose CE-MRI by a factor of 100/x results in poor image quality with widespread noise and ambiguous structures.

The present CNN is trained to reconstruct, from at least a pre-contrast input image and a low dose contrast input image respectively depicting a body part prior to and after an injection of said low dose of contrast agent, a standard dose contrast image depicting said body part after an injection of said standard dose of contrast agent.

Such CNNs are known to the skilled person, see for instance the application WO2019074938 or the document *Ammari S, Bône A, Balleyguier C, et al. Can Deep Learning Replace Gadolinium in Neuro-Oncology? Invest*

Radiol. 2021; Publish Ah(00):1–9. doi: 10.1097/rli.000000000000008, and allow to reduce the contrast agent dose: by applying the CNN to a candidate pre-contrast image and a candidate low dose contrast image depicting a body part prior to and after an injection of only the low dose of contrast agent, a
5 synthetic contrast image simulating said body part after an injection of the standard dose can be generated.

To rephrase, this CNN is able to predict the standard dose contrast image from the pre-contrast image and the low dose contrast image, and hence can be referred as “dose minimization CNN”.

10 Indeed, we can still have the quality of the standard dose contrast image while only injecting the low dose of contrast agent.

Possible embodiments of this CNN and training methods will be described below.

Preferably, said CNN use as inputs as least the T1-weighted pre-contrast/contrast images (and possibly also the T2-flair-weighted pre-contrast
15 image and/or the ADC pre-contrast map) and outputs another T1-weighted contrast image.

The present method proposes a clever use of this dose minimization
20 CNN to virtually increase the dose, by applying the dose reduction CNN on candidate contrast image depicting a body part after an injection of a “first dose” higher than the low dose of contrast agent, possibly up to the standard dose (but not above). This leads to the generation of a synthetic contrast image which is believed to be representative of what would be said body part
25 after an injection of a “second dose” of contrast agent which is higher than the standard dose, i.e. a “super dose”.

Consequently, a very high quality image is obtained, as if a high dose (that could be dangerous to the patient) was injected but with only injecting in reality no more than the standard dose of contrast agent.

30 In other words, the CNN is not used for the task it is actually trained for, which is very unusual, see the two exemplary pipelines of **figure 2**

wherein the standard dose contrast image is directly used as the first dose contrast image.

In this figure, the T1-weighted pre-contrast image is referred to as "T1", the T2-flair-weighted pre-contrast image is referred to as "T2", the ADC pre-contrast map is referred to as "ADC", the low-dose T1-weighted contrast image is referred to as "T1c-", the standard-dose T1-weighted contrast image is referred to as "T1c", the "super dose" T1-weighted contrast image is referred to as "T1c+".

Hypothesizing that the CNN primarily learned to amplify the difference of contrast between their pre-contrast and post-contrast inputs, replacing T1c- by T1c images at inference was expected to synthesize approximate quadruple-dose T1c+ images.

For instance, assuming the low dose (D_c) is $x\%$ of the standard dose (D_c): $D_{c-} = x/100 * D_c$

Because the same CNN is used, the first and second doses (D_1 , D_2) can be written with respect to the same equation: $D_1 = x/100 * D_2$.

And thus: $D_{c-} < D_1 \leq D_c$

$x/100 * D_c < x/100 * D_2 \leq D_c$

$D_c < D_2 \leq 100/x * D_c$, with $D_{c+} = 100/x * D_c$

Consequently, in the embodiment wherein the low dose is 25% of the standard dose, the second dose can reach 400% of the standard dose if the standard dose is used as first dose (see figure 2). In other words, if the standard dose is 0.1 mmol.kg, the second dose can reach 0.4 mmol/kg (virtual supplementary injection of 0.3 mmol/kg) hence the name "super dose".

Note that said first dose is advantageously at least 80% of the standard dose, preferably around 100% of the standard dose, meaning that the second dose is typically at least 160% of the standard dose (80%/50%), preferably at least 240% (80%/33%), and preferably between 320% and 400% of the standard dose (80%/25% and 100%/25%).

Tridimensional UNet

The **figure 3** depicts an exemplary architecture of dose minimization CNN, of the U-Net type. Note that in the case of tridimensional pre-contrast/contrast images, the CNN is itself a tridimensional network as in the example of figure 2, handling quadridimensional feature maps.

U-Net is a neural network of the encoder-decoder type: it comprises an encoder branch (or “contracting path”) that maps the input (at least one pre-contrast image and the low dose image/first dose image) into a high-level representation and then a decoder branch (or “expanding path”) generating the output image (the standard dose image/second dose image) from the high-level representation.

U-Net further comprises skip (or “lateral”) connections between the encoder branch and decoder branch.

The encoder branch, acts as a backbone, and can be seen as a conventional feature extraction network that can be of many types, and in particular a conventional CNN, preferably a fully convolutional neural network (direct succession of blocks of convolution layers and non-linear layers such as ReLU (rectified linear unit), that in particular alternates residual and strided convolution blocks to downsample). The encoder branch extracts from the input image a plurality of initial feature maps representative of the input image at different scales. More precisely, the backbone consists of a plurality of successive convolution blocks, such that the first block produces a first initial feature map from the input, then the second block produces a second initial feature map from the first initial feature map, etc.

It is conventionally understood for convolutional neural networks that the scale is smaller with each successive map (in other words the resolution decreases, the feature map becomes “smaller” and therefore less detailed), but of greater semantic depth, since increasingly high-level structures of the image have been captured. Specifically, initial feature maps have increasing numbers of channels as their spatial size decreases.

In practice, a pooling layer is placed between two blocks to decrease the scale by a factor of 2 (typically 2x2x2 convolution with stride 2 for down

sampling in case of 3D images), and from one block to another the number of filters of the convolution layers used (generally 3x3x3 convolutions) is increased (and preferably doubled).

In the 5-level standard U-Net there is for example successive channel numbers of 32, 64, 128, 256 and 512, and successive map spatial sizes (for a 160x192x160 input image) of 160x192x160, 80x96x80, 40x48x40, 20x24x20, 10x12x10. We see that the input has already 4 channels - 3 pre-contrast images (T1, T2-flair ADC) and 1 contrast image (T1c- in the training and T1c in operation), while the output as a single channel (T1c in the training and T1c+ in operation).

The feature maps obtained by the encoder branch are said to be initial because they will be reprocessed by the decoder branch. Indeed, as explained, "low-level" maps have a higher spatial resolution but a shallow semantic depth. The decoder branch aims to increase their semantic depth by incorporating the information from the "high-level" maps.

Thus, said decoder branch of the CNN has the symmetrical architecture of the encoder branch, as it generates, from the initial feature maps, a plurality of enriched feature maps that are again representative of the input image at different scales, but they incorporate the information from the initial feature maps of smaller or equal scale while reducing the number of channels.

In other words, the decoder branch also consists of a plurality of successive convolution blocks but in opposite order, such that the first block produces the first enriched feature map (from which the output image may be directly generated) from the second enriched feature map and the first initial feature map, after the second block produces the second enriched feature map from the third enriched feature map and the second initial feature map, etc. The decoder branch is also preferably a fully convolutional CNN (direct succession of blocks of convolution layers and non-linear layers such as ReLU, that in particular alternates residual and strided convolution blocks to upsample),

In more details, each i -th enriched map has the scale of the corresponding i -th initial map (i.e. sensibly same spatial size) but incorporates the information of all j -th maps, for each $j \geq i$. In practice, each i -th enriched map D_i is generated according to the corresponding i -th initial map E_i and/or
5 the next $(i+1)$ -th enriched map, hence the “contracting and expansive” nature of the branches (i.e. “U” shaped): the initial maps are obtained in ascending order and then the enriched maps are obtained in descending order.

Indeed, the maximum semantic level is obtained at the “smallest-scale” map, and from there each map is enriched on the way back down again with
10 the information of the already enriched maps. The skip connections between the encoder branch and the decoder branch provide the decoder branch with the various initial maps.

Typically, the generation of an enriched map based on the corresponding initial map and the smaller-scale enriched map comprises
15 rescaling of the enriched map, typically doubling the scale (if there has been halving of scale in the encoder branch), i.e. up sampling of the enriched feature map with by a $2 \times 2 \times 2$ convolution (“up-convolution”) that halves the number of feature channels, then concatenation with the corresponding initial map E_i (cropped of necessary, both maps are now sensibly the same scale)
20 to double again the number of channels, and from one block to another the number of filters of the convolution layers used (generally $3 \times 3 \times 3$ convolutions) is again decreased (and preferably further halved).

Downsampling and upsampling convolution blocks rely on $2 \times 2 \times 2$ kernels, all other kernels are $3 \times 3 \times 3$ at the exception of the final $1 \times 1 \times 1$
25 convolution. All activation functions but the last sigmoid are 0.2-LeakyReLU.

Note that the present invention is not limited to the specific U-Net architecture: could be suitable any CNN which is trained to reconstruct, from at least a training pre-contrast image and a training contrast image respectively depicting a body part prior to and after an injection of said low
30 dose of contrast agent, a training contrast image depicting said body part after an injection of said standard dose of contrast agent.

The training will be described below.

Method for medical imaging

As represented by **figure 4**, the present method starts with a step (a)
5 of obtaining said pre-contrast image and contrast images to be processed
(referred to as candidate pre-contrast and contrast images), in particular T1-
weighted pre-contrast/contrast images, preferably from a medical imaging
device 10 connected to the second server 1b.

The candidate pre-contrast image and candidate contrast image
10 respectively depict a body part prior to and after an injection of a first dose of
contrast agent, wherein said first dose is higher than a predetermined low
dose, the predetermined low dose being lower than a predetermined standard
dose.

In the preferred MRI embodiment, step (a) comprises obtaining three
15 candidate pre-contrast images (the candidate T1-weighted pre-contrast
image, a candidate T2-flair-weighted pre-contrast image, and a candidate
ADC pre-contrast map).

Note that this step (a) may be implemented by the data processor 11b
of the second server 1b and/or by the medical imaging device 10.

20 In a main step (b), implemented by the data processor 11b of the
second server 1b, the CNN is applied to the candidate pre-contrast image
and the candidate contrast image, so as to generate a synthetic contrast
image which is believed to simulate said body part after an injection of a
second dose of contrast agent which is higher than the standard dose.

25 In the preferred MRI embodiment, the CNN is applied to the three
candidate pre-contrast images and the candidate contrast image.

Training method

30 The method advantageously comprises a previous step (a0) of training
the CNN, implemented by the data processor 11a of the first server 1a.

By training, it is meant the determination of the optimal values of parameters and weights of the CNN. Note that alternatively the CNN may be directly taken “off the shelf” with preset values of parameters and weights.

Said training method can be performed according to the prior art, and
5 any suitable training protocol known to a skilled person may be used.

It is here to be understood that the CNN is trained to perform its original “dose minimization” task, i.e. to reconstruct, from at least a training pre-contrast image and a training contrast image respectively depicting a body part prior to and after an injection of said low dose of contrast agent, a training
10 contrast image depicting said body part after an injection of said standard dose of contrast agent.

Indeed, it is impossible to directly train a CNN to generate, from at least a training pre-contrast image and a training contrast image respectively depicting a body part prior to and after an injection of a first dose of contrast
15 agent higher than the lower dose, a synthetic contrast image simulating said body part after an injection of a second dose of contrast agent which is higher than the standard dose: such training would require having training images after an injection of the second dose, thereby making the total injected dosage amount greater than the dosage amount suggested by recent clinical
20 guidelines

By contrast, to learn the “dose minimization” task, the training base has just to comprise a plurality of sequences of at least one training pre-contrast image (as explained there could be possibly three pre-contrast images), an “initial” training contrast image (low dose contrast image) and a “final” training
25 contrast image (standard dose contrast image) respectively depicting a body part prior to, after an injection of said low dose of contrast agent, and after an injection of said standard dose of contrast agent.

The CNN is trained to predict the final training contrast image (as ground truth) from the training pre-contrast image(s) and the initial contrast
30 image of the same sequence.

In more details, for generating a training example, we perform the normal protocol for acquiring a contrast image depicting a body part after an

injection of said standard dose of contrast agent, but the administration of the standard dose is simply split in two successive injections (1) the low dose and (2) the difference between the low dose and the standard dose, for example 0.025mmol/kg and $0.1-0.025=0.075$ mmol/kg of GBCA as explained, and an additional contrast image is acquired in between as the "initial" contrast image, this image actually depicting the body part after an injection of said low dose of contrast agent. Note that two-injection MRI protocols have been recently included in consensus guidelines for glioma imaging, the first injection playing the role of preload bolus for a possible later perfusion sequence. Consequently, it is harmless.

To sum up, for a patient:

- the pre-contrast image(s) is(are) acquired;
- the low dose is injected and a first contrast image is acquired;
- the difference between the standard dose and the low dose is injected (so that the patient receives in total the standard dose), and a second contrast image is acquired;
- the sequence of the pre-contrast image(s), the two successive contrast images is labeled as a training example.

Tests

Figure 5 displays the T2-Flair, T1c, T1c+ and tse-T1c images for four example MRI exams from the test sample, either with brain metastases or glioma. We can see that the T1c+ images (the synthetic super dose contrast images) present an excellent quality and are easier to read.

Table 1 reports average image quality (IQ) scores for the T1c, T1c+ and tse-T1c images from 79 exams of a test sample. Grades are expressed on a 4-point Likert scale ranging from 1 (poor) to 4 (excellent). Standard deviations are given between parentheses. Differences across readers and post-contrast MRI images are compared using two-tailed t-tests, and p-values

are reported. Best metrics are emphasized using a bold font when the 5% significance threshold is met)

This table shows the synthesized T1c+ images were preferred by two readers (neuroradiologists with respectively 10 and 11 years of experience) for their general image quality, when no quality difference was found between T1c and tse-T1c images. On average between readers, T1c and tse-T1c were graded 2.7/4 (average to good), when T1c+ were graded 3.4/4 (good to excellent).

	IQ $\pm$ std (grades on a 4-point scale)			T1c vs. T1c+	T1c vs. tse-T1c	T1c+ vs. tse-T1c
	T1c	T1c+	tse-T1c			
Reader Average	2.7 ($\pm$ 0.5)	3.4 ($\pm$ 0.3)	2.7 ($\pm$ 0.6)	$P < .001^*$	$P = .62$	$P < .001^*$
Reader 1	2.8 ($\pm$ 0.5)	2.9 ($\pm$ 0.4)	2.7 ($\pm$ 0.6)	$P = .02^*$	$P = .36$	$P = .007^*$
Reader 2	2.6 ($\pm$ 0.7)	3.9 ($\pm$ 0.4)	2.7 ($\pm$ 0.8)	$P < .001^*$	$P = .14$	$P < .001^*$
R1 vs. R2	$P = .007^*$	$P < .001^*$	$P = .89$			

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Table 1

Table 2 reports the average contrast-to-noise ratio (CNR), lesion-to-brain ratio (LBR), and contrast enhancement percentage (CEP) performance metrics for the T1c, T1c+ and tse-T1c images from 52 exams of the test sample with at least one reference lesion. Standard deviations are given between parentheses. Differences across readers and post-contrast MRI images are compared using two-tailed t-tests, and p-values are reported. Best metrics are emphasized using a bold font when the 5% significance threshold is met.

With an average CNR of 44.5, LBR of 1.66 and CEP of 112.4%, the synthesized T1c+ images outperform both T1c and tse-T1c images for all the considered metrics.

	T1c	T1c+	tse-T1c	T1c vs. T1c+	T1c vs. tse-T1c	T1c+ vs. tse-T1c
CNR	9.1 ($\pm$ 5.8)	44.5 ($\pm$ 25.7)	16.8 ($\pm$ 9.7)	$P < .001^*$	$P < .001^*$	$P < .001^*$
LBR	1.31 ($\pm$ 0.18)	1.66 ($\pm$ 0.27)	1.44 ($\pm$ 0.24)	$P < .001^*$	$P < .001^*$	$P < .001^*$
CEP	85.6 ($\pm$ 35.5)	112.4 ($\pm$ 36.5)	92.2 ($\pm$ 38.1)	$P < .001^*$	$P = .011$	$P < .001^*$

Table 2

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Finally, the average lesion detection performance reached when reading the T1c images, and when also jointly reading its post-processed T1c+ counterpart, was compared. In both reading scenarios, the pre-contrast T2-Flair image was available to readers as well. A read with access to T2-Flair, T1c and tse-T1c images defined 187 reference lesions with a median long axis length of 9.2mm (inter-quartile range of 10.7mm). Three nested evaluation configurations were considered, depending on the minimum included lesion size: 10mm, 5mm or 0mm – all lesions being considered in this case.

The access to T1c+ images increased the lesion detection sensitivity (SE) for both readers in all evaluation configurations. On average across readers, the overall SE was 75% when T1c+ images were available (59% with T1c images only, $P<.001^*$), 85% for lesions larger than 5mm (70% with T1c, $P<.001^*$), and 96% for lesions larger than 10mm (88% with T1c, $P=.008^*$). No difference was found in terms of FDR (false detection rates), which remained below 0.19/exam across readers, reading scenario, and evaluation configurations. No difference was found between readers for neither SE nor FDR.

PPV remained higher than 90% in all configurations. On average across readers, PPV quantitative differences were 3% at maximum between the two reading scenarios. F1 was higher than 90% across readers and readings for lesions larger than 10mm, higher than 80% for lesions larger than 5mm, and higher 70% when all lesions were included. On average across readers, F1 was higher when T1c+ was available to readers by a margin that varied between 4% and 11% according to considered range of lesion sizes.

Computer program product

In a second and a third aspect, the invention provides a computer program product comprising code instructions to execute a method (particularly on the data processor 11a, 11b of the first and/or second server 1a, 1b) according to first second aspect of the invention for medical imaging,

and storage means readable by computer equipment (memory of the first or second server 1a, 1b) provided with this computer program product.

CLAIMS

1. A method for medical imaging, the method being characterized in that it comprises the implementation, by a data processor
5 (11b) of a second server (1b), of steps of:

(a) Obtaining (i) at least one candidate pre-contrast image and a candidate contrast image respectively depicting a body part prior to and after an injection of a first dose of contrast agent, wherein the first dose of contrast agent is higher than a low dose of contrast agent and the low dose is lower than a standard dose of contrast agent; and (ii) a convolutional neural network, CNN, being trained to reconstruct, from at least one pre-contrast input image and a low dose contrast input image respectively depicting the body part prior to and after an injection of the low dose of contrast agent, a standard dose contrast image depicting the body part after an injection of the standard dose of contrast agent;
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(b) Generating a synthetic contrast image by applying the CNN to the at least one candidate pre-contrast image and the candidate contrast image.

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2. The method according to claim 1, wherein the low dose of contrast agent is between 10% and 50% of the standard dose of contrast agent.

25 3. The method according to one of claims 1 and 2, wherein the first dose of contrast agent is at least 50% of the standard dose of contrast agent.

30 4. The method according to claims 2 and 3 in combination, wherein the low dose of contrast agent is between 1/5 and 1/3 of the standard dose of contrast agent; and the first dose of contrast agent is at least 80% of the standard dose of contrast agent.

5 **5.** The method according to one of claims 1 to 4, wherein the at least one candidate pre-contrast image and the candidate contrast image are acquired by a medical imaging device (10) connected to the second server (1b), in particular an MRI scanner.

10 **6.** The method according to one of claims 1 to 5, wherein the at least one candidate pre-contrast image includes a T1-weighted pre-contrast image and the candidate contrast image is a T1-weighted image.

7. The method according to claim 6, wherein:

 - the at least one candidate pre-contrast image includes the T1-weighted pre-contrast image, a T2-flair-weighted pre-contrast image and an ADC pre-contrast map;

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 - the at least one pre-contrast input image includes a T1-weighted pre-contrast input image, a T2-flair-weighted pre-contrast input image and a training ADC pre-contrast input map;

 - the low dose contrast input image is a T1-weighted contrast image;

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 - the standard dose contrast image is a T1-weighted contrast image;

 - the synthetic contrast image is a synthetic T1-weighted contrast image.

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8. The method according to one of claims 1 to 7, wherein said CNN comprises an encoder branch followed by a decoder branch, with skip connections between the encoder branch and decoder branch.

30 **9.** The method according to one of claims 1 to 8, comprising a previous step of training, by a data processor (11a) of a first server (1a), said CNN from a base of sequences of at least one training pre-contrast image, a first training contrast image and a second training image respectively

depicting a body part prior to, after an injection of the low dose of contrast agent, and after an injection of the standard dose of contrast agent.

5 **10.** Computer program product comprising code instructions
to execute a method for medical imaging according to one of claims 1 to 9,
when said computer program is executed on a computer.

10 **11.** A computer-readable medium, on which is stored a
computer program product comprising code instructions for executing a
method for medical imaging according to any one of claims 1 to 9.