

Retinotopic mapping in the human visual cortex using vascular space occupancy-dependent functional magnetic resonance imaging

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Recently, we introduced a new methodology, vascular space occupancy functional magnetic resonance imaging, which detects brain activation on the basis of blood volume changes in parenchymal microvasculature and may provide higher spatial specificity than the blood oxygenation level-dependent method. To study whether this technique can be used for advanced brain mapping applications, we performed retinotopic mapping using alternating horizontal and vertical wedges that stimulate different portions of the visual field. The results using vascular space occupancy functional magnetic resonance imaging showed clear boundaries for VI/V2/VP/V4v in

the ventral areas and VI/V2/V3/V3A in the dorsal areas, similar to the maps obtained using blood oxygenation level-dependent functional magnetic resonance imaging. Vascular space occupancy functional magnetic resonance imaging is a useful addition to the other neuroimaging techniques. Disadvantages of vascular space occupancy functional magnetic resonance imaging include lower contrast-to-noise ratio (about 1/3 of that of blood oxygenation level-dependent method) and limited volume coverage (nine slices for TR=3 s). *NeuroReport* 16:1635–1640 © 2005 Lippincott Williams & Wilkins.

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Introduction

Cerebral blood volume (CBV), defined as the volume fraction of blood in the brain, is an important hemodynamic parameter and is known to be focally modulated during brain activation [1]. Therefore, CBV can be used as a physiological contrast for functional brain mapping. As the vasodilatation during brain activation occurs predominantly in microvasculatures (diameters <100–200 μm) and is not present in large venous vessels [1,2], brain mapping studies using CBV have shown improved spatial localization over the blood oxygenation level-dependent (BOLD) method in various applications [3–6]; for instance, in distinguishing columnar organizations [5,6] and cortical layers [4]. These studies all required invasive procedures such as injection of potentially toxic contrast agents or opening of cranial windows, and are therefore not feasible in awake humans. Recently, we introduced a technique, vascular space occupancy (VASO)-dependent functional magnetic resonance imaging (fMRI), that can non-invasively detect focal changes in CBV during activation [7–9]. Our previous studies using simple visual stimulation have

shown that this method can better localize the brain parenchyma and suppress large vein contributions [7]. VASO fMRI has also been applied to the study of quantitative interpretation of BOLD signal [10] and to understanding the mechanism of cerebrovascular responses during neuronal activity [9,11].

To date, however, the feasibility of VASO fMRI for advanced brain mapping applications has not been evaluated. Extension of an fMRI technique from simple paradigms (e.g. checkerboard visual stimulation, finger tapping, hypercapnia, etc.) to more complicated neuroscience-relevant applications is not trivial. Many non-BOLD fMRI techniques were proposed during the past decade but were not widely used in neuroscience applications because of factors such as requirement of contrast agent injection, difficulty in paradigm timing and limitation in hemodynamic response. The VASO technique also suffers from certain limitations, including low sensitivity and restricted volume coverage [7]. Recent availability of high-field magnetic resonance systems has improved the contrast-to-noise ratio (CNR) of VASO fMRI [10]. In addition, new pulse

sequences have been developed to allow multi-slice acquisitions without increasing the scan durations [8]. Although the time efficiency of the VASO method (about 10 slices with a TR of 3 s) is still lower than that of BOLD (about 30 slices with a TR of 3 s), this technique may find applications in studies in which a particular brain region is the primary focus.

Early visual areas in the cerebral cortex are known to be retinotopically organized [12]. Such precise spatial correspondence between visual field and cortical surface has been widely studied using the BOLD technique [13–15]. In principle, this mapping should also be achieved using the VASO method. To evaluate this, here we investigated the feasibility of using VASO fMRI for retinotopic mapping in the human visual cortex. To our knowledge, this is the first report demonstrating that a non-BOLD fMRI technique can be used successfully to generate retinotopic maps in the human cortex, providing an alternative approach to study the cortical organization in human visual cortices.

Materials and methods

Magnetic resonance imaging experiment

Studies were performed on a 3T magnetic resonance scanner (Philips Medical Systems, Best, The Netherlands) using body coil transmission and sensitivity encoding (SENSE) head coil reception. The protocol was approved by the Institutional Review Board of Johns Hopkins University (Baltimore, Maryland, USA). All study participants ($n=6$, two men, four women, age range 24–39 years) gave informed, written consent before taking part in the study. Visual stimuli for retinotopic mapping consisted of 18 s of vertical wedges (polar angle=30°, diameter=25° visual angle) interleaved with 18 s of horizontal wedges (Fig. 1a), often referred to as meridian mapping stimuli, and was repeated eight times. Such stimuli result in two activation patterns, corresponding to vertical and horizontal wedge stimulations. Owing to the intrinsic mirror representation of the visual field in early visual areas [13], it is known that the center line of each activation pattern specifies the boundary between adjacent visual areas. Multi-slice CBV-based fMRI was performed using a MAGIC-VASO sequence [8] with the following imaging parameters: gradient-echo echo planar imaging, TR=3 s, TI=822 ms, TE=8.7 ms, flip angle (FA)=90°, matrix=80 × 80, SENSE factor 2, FOV=240 mm, nine slices (3 mm thickness, no gap). Gradient-echo BOLD experiments (TE=45 ms) were performed with an identical stimulus paradigm and geometric parameters. Each functional experiment lasted for about 5 min. The VASO experiments were repeated four times to improve signal-to-noise ratio. A three-dimensional magnetization-prepared rapid gradient echo (MPRAGE) image (TR/TE/FA=8.2 ms/3.9 ms/8°, resolution 1 × 1 × 1 mm³, scan duration 6 min 30 s) was acquired for anatomical reference and was used for overlaying functional data. In one group of participants ($n=3$), the slice orientation for functional scans was coronal, covering the occipital lobe. In a second group of participants ($n=3$), the slices were positioned (obliquely axial) to be parallel to the calcarine sulcus.

Data processing

Data were processed on a PC using BrainVoyager (Brain Innovation, Maastricht, The Netherlands). The pre-proces-

ing of the functional data included three-dimensional motion correction, baseline drift correction, spatial smoothing (full-width at half-maximum=4 mm) and coregistration with the MPRAGE image. The data were then spatially transformed into Talairach coordinates, and automatic segmentation of gray and white matter was conducted using the MPRAGE image. To facilitate the delineation of shapes and sizes of different visual areas, the cortical surface was inflated for activation overlay. For activation detection, a series of cross-correlation coefficients were calculated between the signal time-course (Fig. 1a) and temporally shifted stimulus paradigm (shift range=−1–7 timepoints) [16], which gives a total of nine cross-correlation coefficient values. The activation map was then color coded (Fig. 1b and Fig. 2) according to the phase shift at which the maximum cross-correlation coefficient was achieved. This coding scheme can distinguish cortical regions corresponding to the two wedges. Ideally, the horizontal wedge stimulation should produce maximum cross-correlation coefficients at shift=0, while the vertical wedge should correspond to shift=6 (block duration/TR=18 s/3 s=6 points). To allow for noise contamination and hemodynamic response variations, the shift range was extended from {0,6} to {−1,7}, which resulted in the horizontal wedges coded in red-yellow (Fig. 1b) and vertical wedges coded in blue-green.

Spatial correspondence between the VASO and BOLD maps was quantitatively evaluated by their joint histogram. Shown in Fig. 1b is an example illustrating how the joint histogram was calculated. For each point in the retinotopic maps, the corresponding colors for VASO and BOLD were obtained and converted to a shift index ranging from −1 to 7. The VASO shift was then used as y -coordinate and the BOLD shift as x -coordinate, and this was mapped to a node on a 9 × 9 grid. Note that different points in the color map can be mapped to the same node. This procedure results in a two-dimensional histogram (Fig. 3), on which the value of each node indicates the frequency of occurrence that the points in the color map have a VASO shift of y and a BOLD shift of x .

Results

Figure 2a shows the VASO activation map color coded according to the scheme specified above. The voxels are clustered into separate color groups corresponding to the two types of stimulations. Figure 2b shows the activation maps overlaid on an inflated cortical surface in the left hemisphere of a brain. The dark grayscale indicates sulci regions and the bright grayscale indicates gyri regions. The regions in and around the calcarine fissure are known to contain the early visual areas. Two viewing angles, medial view (top row) and posterior view (bottom row), are shown to visualize the ventral and dorsal part of the retinotopic maps, respectively. Both techniques show multiple retinotopic representations of the visual field in the early visual areas: ventral maps include V1, V2, VP and V4v; dorsal maps include V1, V2, V3 and V3A. As can be seen, the VASO and BOLD maps have similar general patterns with interleaved stripes of red-yellow patches and blue-green patches. Comparing ventral and dorsal maps, it was found that the ventral maps are in general more robust than the dorsal ones. This was the case for both VASO and BOLD methods.

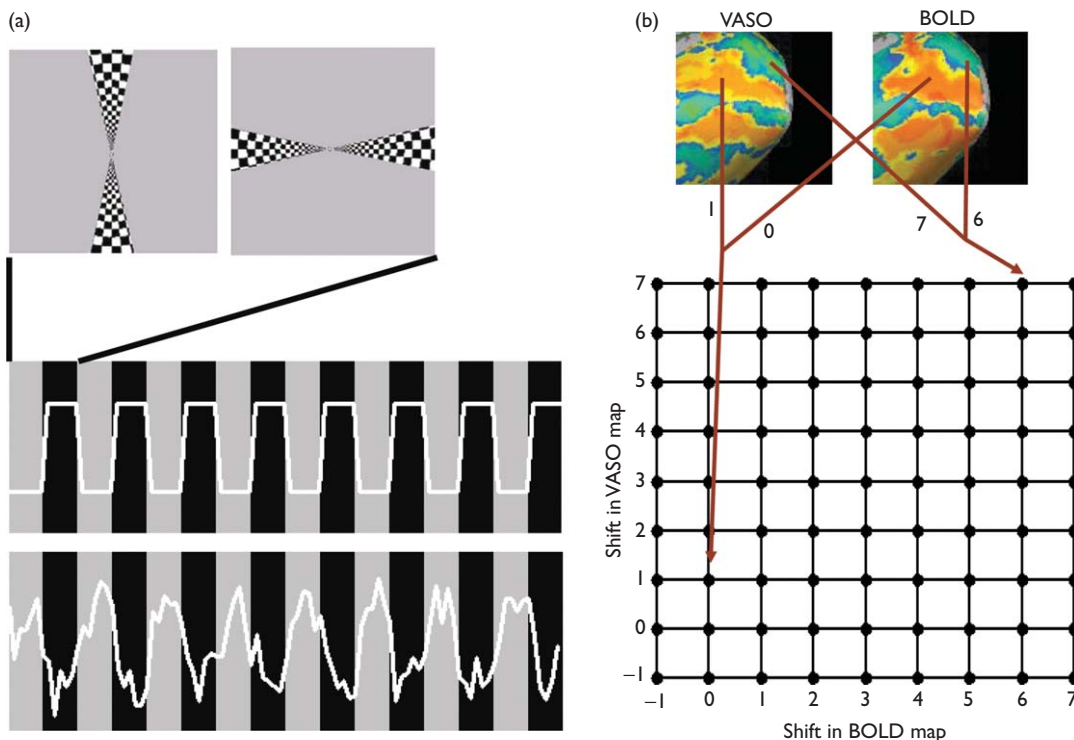


Fig. 1 (a) Stimulus paradigm used for retinotopic mapping. Stimuli consist of 18 s of flashing vertical wedges interleaved with 18 s of flashing horizontal wedges. The bottom panel shows a typical vascular space occupancy (VASO) signal time-course in a brain region responding to the horizontal wedges. The curve appears antiphased to the stimulus paradigm because VASO shows a signal decrease on activation. (b) Diagram illustrating the calculation of joint histogram between VASO and blood oxygenation level-dependent (BOLD) activation maps. For each point in the map, the color coding is first converted to a shift index ranging from -1 to 7 . Then the VASO shift is used as y-coordinate and BOLD shift as x-coordinate. Two examples are given. The point in the orange region has a VASO shift of 1 and a BOLD shift of 0 , thereby corresponding to the node $\{0,1\}$. The point in the green region has a VASO shift of 7 and a BOLD shift of 6 , thereby corresponding to the node $\{7,6\}$. The value of a given node in the joint histogram is proportional to the number of points mapped to this node. The color maps shown are from a right hemisphere viewing from the medial side.

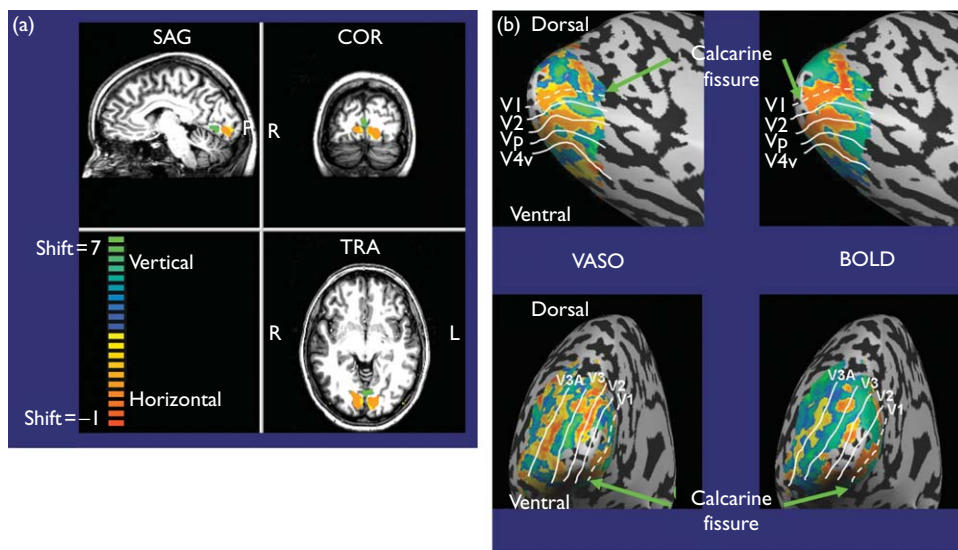


Fig. 2 (a) Representative color map coded by the shift value at which a maximum cross-correlation coefficient with the stimulation paradigm is achieved. Red-yellow color corresponds to horizontal wedges and blue-green color corresponds to vertical wedges. (b) Vascular space occupancy (VASO) (left) and blood oxygenation level-dependent (BOLD) (right) retinotopic maps overlaid on an inflated cortical surface of a left hemisphere. Top row: medial view. Bottom row: posterior view.

Figure 3 shows the joint histogram of VASO and BOLD maps averaged over the participants with coronal slice orientation ($n=3$, six hemispheres). Two peaks can be clearly

seen: one around $\{0,1\}$ and the other around $\{6,6\}$. This result shows that the shift indices of VASO and BOLD maps each form two separate groups, and the group classification

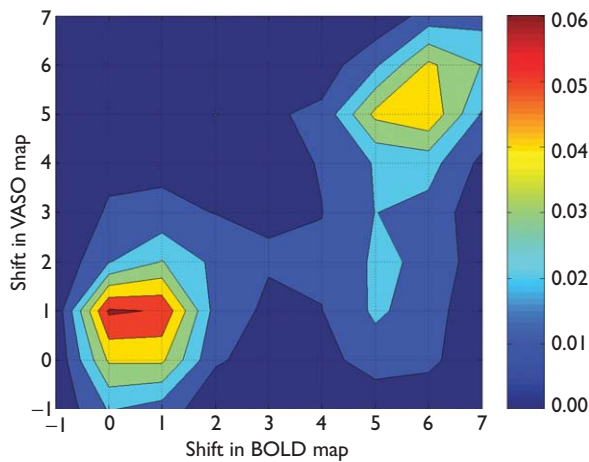


Fig. 3 Averaged joint histogram ($n=3$, with six hemispheres) showing the spatial correlation between the maps obtained with the two techniques. The plot has been interpolated to show the contours. The values indicate the fractions of voxels with the given shift indices, and are color coded according to the color bar shown on the right. One peak, centered around $\{0,1\}$, corresponds to the horizontal wedges. The other peak, centered around $\{6,6\}$, corresponds to the vertical wedges.

using these two independent techniques correlates well with each other. The sizes of the groups are $34 \pm 11\%$ (mean \pm SD) of the total cortical area for horizontal wedge (shift range -1 to 2) and $31 \pm 12\%$ of the total cortical area for vertical wedge (shift range 4 to 7). No significant difference was seen between the areas ($P=0.7399$, paired t -test).

Discussion

In this study, we applied a newly developed fMRI technique, VASO, to study the retinotopic mapping in awake humans. The VASO method is sensitive to the changes in microvascular blood volume during neuronal activation, and therefore has a different physiological basis from BOLD. Furthermore, these blood volume changes are known to occur at a very fine spatial scale [1] and promise to provide more localized activation detection than that of BOLD [5–7]. Our results show that it is feasible to use VASO for retinotopic mapping with typical fMRI setup (e.g. at typical magnetic field strength with standard gradient coils and radio frequency coils), and this suggests that VASO fMRI is a useful technique for advanced brain mapping. It should be noted that care must be taken in deciding whether to choose the VASO method or the more conventional BOLD method for a certain application. VASO is known to have lower sensitivity, therefore more averages (i.e. longer scan durations) are needed to match the CNR of BOLD data.

As shown by the joint histogram analysis (Fig. 3), there is no visually discernable difference between the results using the two methods. Although the CBV-based contrast is expected to provide better localization of the activations, the lack of superiority for VASO maps is likely attributed to the relatively large voxel size ($3 \times 3 \times 3 \text{ mm}^3$) used in the present study. Higher spatial resolution in combination with higher field strength (to compensate for the signal loss due to smaller voxels) may be able to elicit the difference.

An additional feature of the VASO technique is that it uses a T1-weighted magnetic resonance pulse sequence and, therefore, the image characteristics are different from those of BOLD (Fig. 4), which is a T2*-weighted sequence. As a result, the VASO fMRI is not subject to signal voiding due to the susceptibility effect in the regions close to air cavities, which is a well known problem in BOLD images (solid arrows, Fig. 4). Therefore, VASO is expected to be particularly useful in studies of frontal or temporal lobe activations.

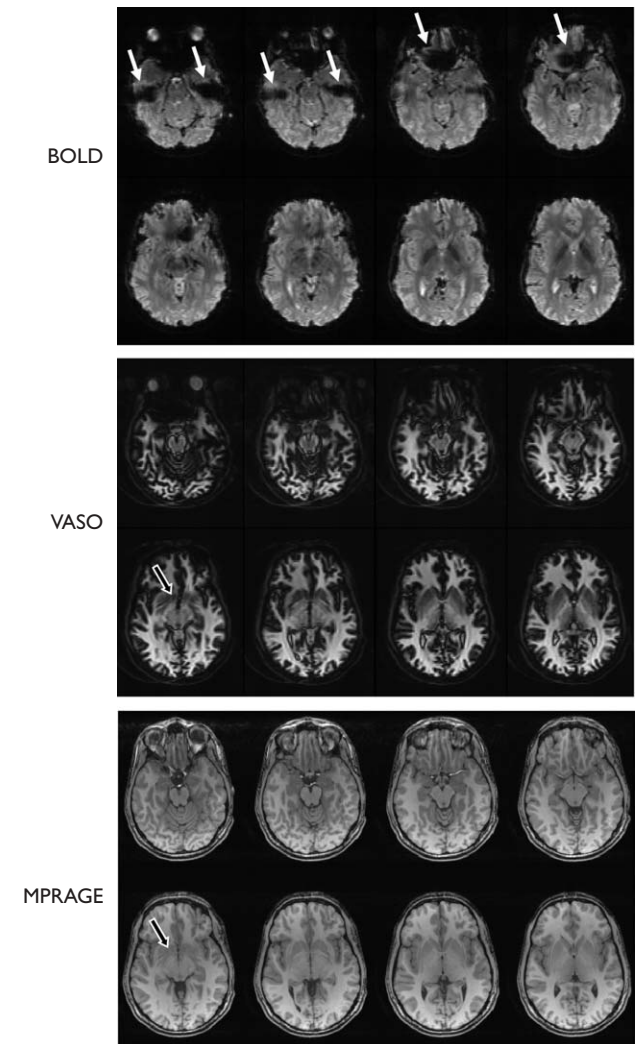


Fig. 4 Blood oxygenation level-dependent (BOLD) (top panel), vascular space occupancy (VASO) (middle panel) functional images and magnetization-prepared rapid gradient echo (MPRAGE) (bottom panel) anatomical images covering the frontal and temporal lobes. The BOLD and VASO images used single-shot echo-planar imaging acquisitions with identical slice positions. The MPRAGE images were acquired in three-dimensional mode but reformatted to the positions of the functional images. In the occipital regions, both BOLD and VASO showed little artifact. In the frontal and temporal regions, however, the BOLD images showed signal voiding in tissue-air interfaces (solid arrows), which is not present in the VASO images. It should be noted that VASO images still contain image distortions (open arrows) in certain regions because of the single-shot echo-planar imaging acquisition scheme. Such distortions are not present in non-echo-planar imaging anatomical images.

It should be pointed out that the VASO method has lower sensitivity than BOLD. A comparison between these two techniques at 1.5T has shown that the CNR of VASO is about 1/5 of that of BOLD at a voxel size of $4 \times 4 \times 10 \text{ mm}^3$ and this ratio increases to 1/3 at a voxel size of $2 \times 2 \times 5 \text{ mm}^3$ [7]. At 3T, the VASO CNR was found to be 43% of that of the BOLD at a voxel size of $2 \times 2 \times 5 \text{ mm}^3$ [10]. In the current work, the VASO experiments were repeated four times to improve the sensitivity so that the final data set would have comparable CNR to that of BOLD, which would allow the map differences mainly reflecting differences in physiological mechanisms rather than sensitivities. Assuming that the data acquired in separate experiments are independent, this would correspond to a 100% increase in CNR. Under this condition, however, the BOLD CNR is still expected to be higher than the VASO CNR. Therefore, lower sensitivity is the main disadvantage of the VASO technique, which also makes it difficult to perform a direct comparison between the VASO and BOLD results.

Technical considerations

In this study, although the stimulation used a block paradigm rather than the commonly used rotating wedge stimulus, a paradigm-shifting data processing strategy [16] was still employed for activation detection and visualization. One can, in principle, simply calculate the cross-correlation between signal time curve and stimulus paradigm, and apply positive and negative thresholds on the coefficients. As a result of time delay in vascular response as well as possible effects of anticipation, however, not all voxels have peak cross-correlation coefficient values at shifts of 0 or 6, as can be seen in Fig. 3. Therefore, by allowing a range of shift values, the small time-course shifting from such confounding factors can be accounted for. In Fig. 3, the peaks appear to have a broader dispersion in the VASO direction than in the BOLD direction. This is especially apparent for the right half of the plot. While the precise explanation for this observation is not clear, two possible reasons are speculated. First, this mismatch between BOLD and VASO may be related to the different physiological mechanisms and their spatial point-spread functions. The BOLD is known to have a large response area due to the draining vein effects [17,18], which can spread the fMRI-detected area to regions where there are no neuronal activations but which contain venous vessels originating from activated tissue. This mechanism of increased response area is not present in the VASO method [7], which only reports regions with vasodilatation. Given the stimulation wedge angles (30°) used in this study, a considerable portion of the visual field is not stimulated by either stimulus. Thus, it is reasonable to expect a fraction of voxels with shift indices spreading randomly from -1 to 7 . Therefore, the mismatch voxels (e.g. in the lower right corner of Fig. 3) may be the voxels that correspond to unstimulated regions, which were falsely classified in BOLD fMRI because of draining vein effects. A second possible reason is that the lower sensitivity of the VASO technique caused the misclassification in the VASO results. In the current study, owing to limited slice numbers ($3 \text{ mm} \times 9$ slices), both coronal and axial slice orientations were tested for VASO retinotopic mapping. Although the results were generally similar, it was found that the coronal slice orientation provides better coverage for the polar angle mapping used

here. For eccentricity mapping, however, it is expected that the axial slice orientation will become advantageous in terms of brain coverage.

Conclusion

VASO fMRI, a CBV-based brain mapping technique, was applied to study the retinotopic representation of human visual cortex. The results show excellent delineation of early visual areas and illustrate the potential of the VASO method for other cognitive neuroscience applications. A joint histogram showed that there is a general agreement between the VASO and BOLD activation maps at a voxel size of $3 \times 3 \times 3 \text{ mm}^3$. VASO fMRI provides a useful alternative to the conventional BOLD-based contrast, and the absence of signal voiding artifacts and the higher spatial specificity of the CBV change may offer unique advantages in some applications.

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