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CGE와 TRFGE 기법으로 얻은 뇌기능 영상에서 혈류효과와 자화율 효과의 해석

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=Abstract=

Analysis of Inflow and Susceptibility Effects in fMRI Obtained by CGE and TRFGE Techniques

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Functional imaging based on the susceptibility only is achieved by separation of the susceptibility effect from the mixture of flow effect by use of a tailored RF pulse in conjunction with gradient echo sequence. Using the tailored RF pulse the susceptibility enhanced functional imaging appears to be explicitly related to the deoxygenation processes, while in the conventional gradient echo technique functional contrast on T2* effect images appear to be mixed with a significant fraction of blood flow (inflow) signals of both arterial as well as venous bloods due to the nature of the fast sequence employed with the gradient echo technique. In this paper, using the tailored RF pulses, one can unambiguously separate the susceptibility and flow effects in functional imaging. Since the signal obtained can be made sufficiently high and represents oxygenation process more accurately, it seems possible to study quantitative oxygen metabolisms in brain function hitherto difficult to do with other gradient echo techniques.

Key words : Functional imaging, Tailored RF pulse, Inflow effect, Susceptibility effect

INTRODUCTION

The sensitivity of a MR gradient echo imaging to susceptibility provides a means to detect oxygenation difference due to the paramagnetic deoxyhemoglobin produced in the capillary[1~3]. Using the changes in image intensity, which is believed to be dependent on the oxygenating states, human brain functional imaging has been studied recently using gradient echo techniques which are generally sensitive to the local magnetic susceptibility[4~10]. However, the conventional gradient echo technique with a short repetition time is also sensitive to the in-flow effect of blood such as arterial as well as venous blood. In most of the functional imagings carried out so far, the changes in image intensity are believed to be dependent on the susceptibility during the external stimulation. However, it is also well known that there is a large in-flow effect, that is, the signal due to fresh unsaturated spins entering into the imaging

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slice, thereby complicating the analysis of the functional image data[4]. Therefore, conventional gradient echo-functional magnetic resonance imaging (CGE-fMRI) appears to be generating the signal which is a mixture of the in-flow effect and susceptibility effect. In the conventional gradient echo sequence, it has been shown that the signal change is affected by a number of factors such as the RF flip angle α, echo time TE, repetition time TR, rate of in-flow, as well as the strength of the susceptibility effect. In other word, in-flow and susceptibility effects are strongly affected by above three parameters, namely flip angle (α), echo time (TE), and repetition time (TR). Although we have obtained susceptibility affected-signal change by the CGE technique with small flip angle and long echo time, the results so far obtained are relatively poor in signal to noise ratio and appear to be contaminated by large fraction of in-flow effect. It is, therefore, unclear to what extend the in-flow effect is mixed with susceptibility effect.

Recently, the tailored RF pulse which is sensitive only to the susceptibility has been developed and applied to NMR venography[1, 2]. Note that in all the normal imaging sequences, susceptibility affected signals are reduced due to spin dephasing. In the tailored RF pulse sequence, the image signals affected by the susceptibility are enhanced while the other signals such as the ones from normal tissues are all suppressed. This signal void or attenuation has been the main mode of contrast mechanism of what is called susceptibility functional imaging. In this paper, the tailored radio frequency gradient echo (TRFGE) sequence is applied to functional imaging in an attempt to quantitatively observe susceptibility alone without the in-flow effect. As will be reported, by using the proposed tailored RF gradient echo-functional magnetic imaging (TRFGE-fMRI), a true susceptibility measurement, which is not mixed with in-flow effect of bloods especially from arteries have been achieved. The latter is a unique advantage of the TRFGE method compared with other gradient echo techniques where large in-flow effects always appear mixed with true oxygenation measurement[4, 5]. We have compared and analyzed systematically both CGE and TRFGE by varying flip angle, repetition time, and echo time. Experimental results obtained with a 2.0 T MR scanner indicate that the observation of the pure susceptibility effect is limited in CGE technique due to the in-flow effect, however, with TRFGE technique most of images obtained appear to be free from in-flow effect.

THEORY

A. Signal Intensity and the Susceptibility Effect

The signal intensity from a voxel surrounded by materials having different magnetic susceptibilities is reduced due to spin dephasing within the voxel. Let us first analyze the relationship between the intravoxel signal intensity and the phase distribution generated by the susceptibility effect and assume that the slice thickness (along the z-direction) is relatively thin so that the field induced within each voxel is linear. In this circumstance the phases of the spins in the voxel will be distributed linearly, that is, the spin phases become either incoherent or dephased, otherwise inphased, under the constant field. The phase distribution in the slice selection direction (z-direction) due to the susceptibility-induced field variation in gradient echo imaging can then be given as

$$\theta_{sus}(z) = \gamma T_E G_{sus} z \tag{1}$$

where γ is the gyromagnetic ratio, T_E is the echo time, Gsus is the field gradient created by the susceptibility difference between the paramagnetic substance and the surrounding tissue, z is the position in the selected slice. Then phase gradient induced by the susceptibility effect, then can be defined as

$$P_{sus}(z) = \gamma T_E G_{sus}. \tag{2}$$

This phase gradient is a result of the combined effect of susceptibilities within both a voxel and a pulse sequence and is an externally controllable parameter, for example, by use of an applied selection RF pulse.

As is known, the RF pulse used in conventional gradient echo imaging is a sinc shaped pulse and has a constant phase distribution in the slice-selection direction. Therefore a constant phase distribution will develop for the normal tissue but a strong linear phase distribution will develop in a voxel affected by susceptibility (see Figs. 1a and 1b). In

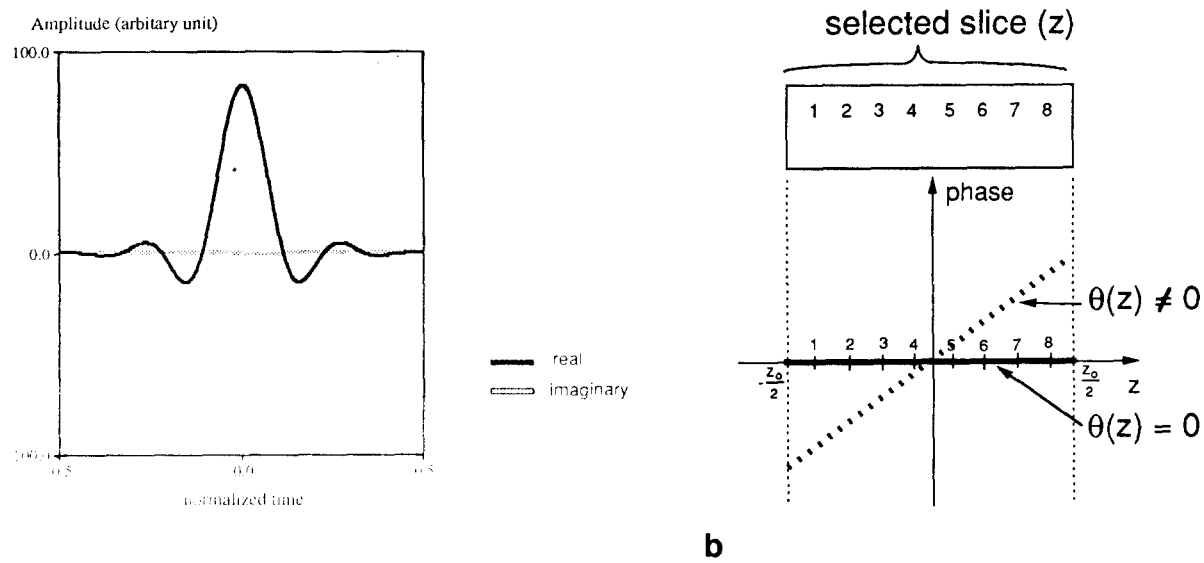


Fig. 1. A conventional RF pulse **(a)** and its phase distribution within the selected slice **(b)**.

the latter, the spins are affected by the linear gradient due to the susceptibility and their phases will be dephased, resulting in intravoxel signal attenuation (see Fig. 1b with dotted lines). The intravoxel signal, S, as a function of the susceptibility-induced phase gradient can then be written as

$$S = \left| \int_{-\infty}^{\infty} M_{rect}\left(\frac{z}{z_0}\right) \exp(iP_{sus}z)dz \right| \tag{3}$$

where M is the magnetization, z_0 is the slice thickness, and $rect(z/z_0)$ is the rectangular function with a width of z_0. In this case, we have assumed that resolution in the transverse (x, y) direction are much higher than the resolution in the slice-selection direction (z) and it is also normalizes so that the signal from the voxel is simply the integration of the magnetizations within the selected slice thickness. By Fourier transform, under the assumption that P_{sus} is a variable, Eq.(3) can be rewritten as

$$S = M_{z_0} \left| sinc\left(\frac{P_{sus}}{2\pi} z_0\right) \right| \tag{4}$$

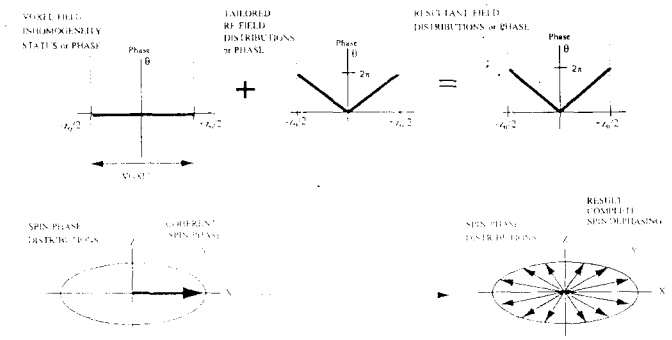
According to Eq.(4), the intravoxel signal decreases with increasing phase gradient (P_{sus}) and in addition signal voids are present at each phase gradient of $\pm 2\pi N/z_0$, where N is integer. This means that the image contrast is strongly affected by susceptibility. Consequently, if gradient echo imaging is used, the susceptibility effect will appear as a signal void or a dark area because of this intravoxel signal attenuation. The signal loss due to the susceptibility will be particularly visible, for example, in the interfaces between the air and normal tissue[11]. As will be elaborated upon, perhaps the most important indication from Eq.(4) is the potential for modifying or utilizing the phase gradient P_{sus} in a voxel by superimposing an RF pulse which has a particular phase gradient so that the resultant phase gradient becomes a desired phase distribution in the selected voxel.

B. CGE Technique

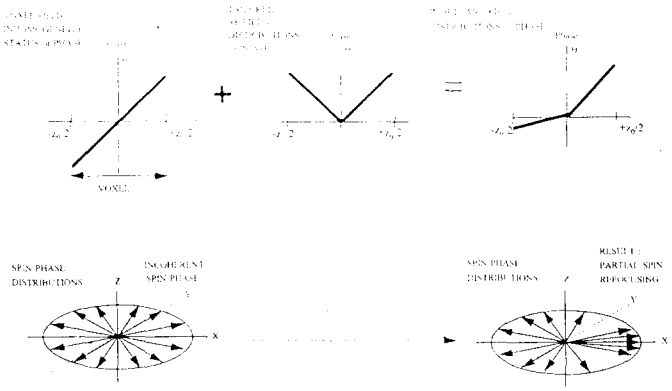
Steady-state free precession (SSFP) or gradient echo imaging techniques has been widely used for the time course study in functional MR imaging (fMRI). In this case the transverse magnetization *M* which generate echo signal by SSFP technique is given by

$$M = M_0 \frac{1-\exp(-TR/T1)}{1-\cos(\alpha)\exp(-TR/T1)} \sin(\alpha)\exp(-TE/T2) \tag{5}$$

Equation(5) indicates that if the repetition time is shorter



a



b

Fig. 2. (a) Resultant phase distribution of spins and spin phase diagram in the voxel of normal tissues when tailored RF pulse is applied. The net phase or signal produced in the voxel is zero due to cancellation. z_0 is the slice thickness.

Fig. 2. (b) Resultant phase distribution of spins and spin phase diagram in the voxel due to superposition of the phase affected by the tailored RF pulse and susceptibility gradient therein. The net phase or signal produced in the voxel is not zero. z_0 is the slice thickness.

than the T1 relaxation time, resultant magnetization would be small. In other words, static spin signal is suppressed, but if flowing spin exists, i.e., the unsaturated flowing spins entering into the selected slice signal will be generated unlike the static tissues. This appears the basic inflow signal enhancement mechanism. This inflow effect in gradient echo, however, is affected by several factors such as the flip angle α, echo time TE and repetition time TR. It is, therefore, strongly suspected that the flow effect plays an important role in gradient echo functional imaging where TR and TE are usually short while α is kept relatively large. Although, the inflow effect is an important indicator of the physiological and functional behaviors in relation to the external sensory stimulations, it is believed to be of no direct relation to the oxygen level or susceptibility effect. It is an independent factor likely to be observed when the imaging slice or selected region contains large veins, for example relatively large veins near the visual cortex in case of visual stimulation. If, therefore, pure oxygen level or deoxyhemoglobin level measurement is the prime importance, inflow effect would appear as a nuisance and if possible should either be eliminated or at least measurable so that desired correction can be made.

C. TRFGE Technique

A tailored RF pulse is designed such that it possesses a bi-linear phase distribution centered around the middle of the selected slice as shown in Fig. 2.[1)] Effect of this TRFGE imaging[1, 2)] is dephasing of the spins in the selected slice if the field is homogeneous as in the case of normal tissues where no strong susceptibility dependent field gradients exist. In Fig. 2(a), this dephasing effect for the case of susceptibility free case such as normal tissue is shown. This characteristic of the tailored RF pulse equally applies to the flowing spins as long as they do not posses susceptibility effects. This technique (TRFGE) is, therefore, effective in suppression of the signals from both stationary tissues as well as flow especially the arterial blood. The resulting signal obtained comes, therefore, only from the susceptibility affected flow such as venous blood both from large vessels as well as small capillaries. Simplified illustrations of the resulting phase distribution expected in the selected voxel when tailored RF pulse is applied in the gradient echo is shown in Fig. 2(b). In Fig. 2(a), the net phase distribution is zero when the tailored RF pulse is applied. However, when the field within the thickness of a selected slice or voxel appears as a linear gradient due to the susceptibility effect, the resulting phase distribution from superposition of the tailored RF and the susceptibility dependent field gradient will be the rephased. In general the signal intensity follows the relation given by

$$S = |2\pi M z_0 \, \mathrm{sinc}\left(\frac{P_{sus}}{2\pi} z_0\right) * F^{-1}\left[\exp\left(i\frac{4\pi}{z_0}|z|\right)\right] \qquad (6)$$

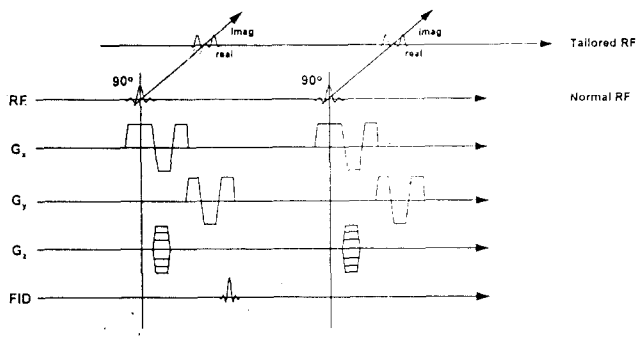


Fig. 3. Conventional gradient echo(CGE) and Tailored RF gradient echo(TRFGE) sequences with first-order gradient moment nulling used in the experiments.

where M and P_{sus} are the magnetization and susceptibility phase gradient, respectively, and * represents the convolution operator. The unique feature of this result is that, on the contrary to the case of normal tissues, the signal intensity will increase linearly with increasing phase gradient value. Using this fact, susceptibility effect enhanced imaging using TRFGE technique can be accomplished.

For functional imaging using the TRFGE sequence, therefore, the signal from the visual cortex would decrease during external stimulation since the oxygenation in the capillary is increasing, thereby decreasing the susceptibility effect. On the other hand, during the rest period, the signal from the visual cortex would increase because of the increased deoxgenation of the capillary. Therefore, the signal changes during the time course by TRFGE-fMRI is basically opposite from that of the CGE-fMRI, i.e. TRFGE-fMRI gives a large signal if susceptibility increases instead of decreasing. Advantage of this reverse characteristic compared with CGE is obvious. For instance, the susceptibility effect alone can be observed without interference from the other background signals such as that that from normal tissues. As is known, the signal changes in CGE-fMRI is likely that during the stimulation the signal from the cortex is increasing compared with rest because of the increase of fresh(arterial) blood supply which in effect believed to reduce local susceptibility effect in the conventional gradient echo sequence. The problem with the CGE technique is that both the oxygenation and blood flow are proportional, i.e., the in-flow effect is proportional to the susceptibility decrease. The time course data obtained with the TRFGE sequence is, therefore, not only different, but is opposite in comparison to the CGE sequence.

Furthermore, the obvious advantages of the TRFGE sequence is that the method is insensitive to the in-flow effect, especially to the arterial bloods which are usually fast flow and believed to be primarily responsible for the in-flow effect in the conventional gradient echo imaging. This is because of the fact that the arterial bloods have no susceptibility effect, therefore, spins will be dephased just like normal tissues. Although, the TRFGE technique is still affected by in-flow effect of venous blood, the effect is negligibly small due to the slow velocity of the venous blood. On the contrary, in CGE imaging, the signal change is not only affected by the susceptibility but is also affected by the in-flow effect of the blood flow of both arterial and venous bloods. In the CGE sequence, therefore, signals are changing according to the RF flip angle α, TE, and TR, as well as to both susceptibility and in-flow effect. For example, in CGE, the susceptibility contrast increases with the increase of echo time, but the signal loss(both susceptibility contrast signal and inflow effect signal) also increases thereby decreasing overall SNR. As has been discussed, this apparent controversy can be overcome by use of the TRFGE technique in which susceptibility contrast is independent of TR and flip angle a as well as TE.

EXPERIMENTAL RESULTS AND DISCUSSIONS

A series of TRFGE and CGE experiments with varying a, TE, and TR were performed on a 2.0 Tesla whole body MRI system with a surface coil. In Fig. 3, the CGE and TRFGE sequence with added first-order gradient moment nulling used in the experiments was plotted. Functional imaging was carried out by photic stimulation. Concurrently, a series of corresponding experiments using the CGE imaging sequence were also carried out and compared with the TRFGE technique. For the time course studies, flip angles of 30° to 90°, repetition times of 35 to 65 msec, and echo times of 16 to 35msec were used. An imaging time of

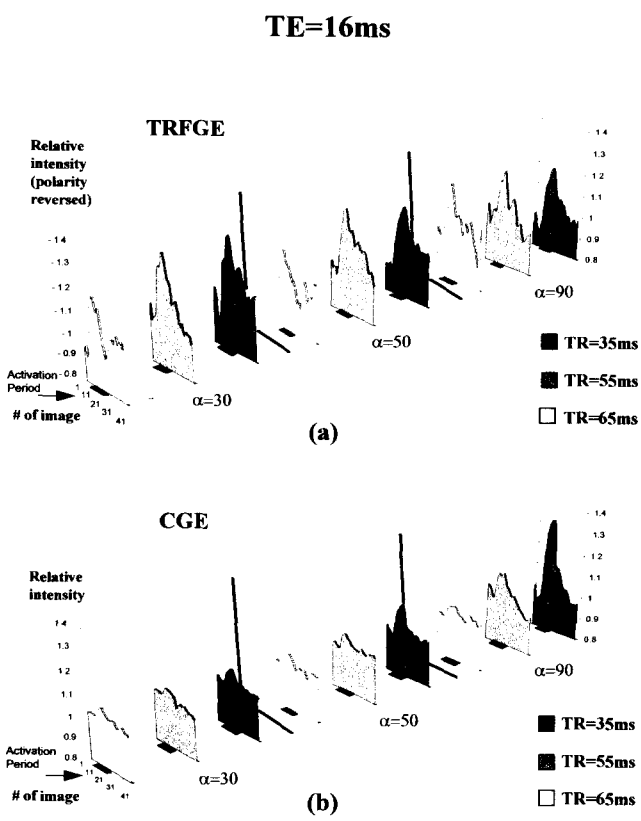


Fig. 4. (a) Data obtained by the TRFGE sequence with varying the RF flip angle α(30° to 90°) and repetition time(35msec to 65msec) for a fixed TE(16msec). **(b)** Same time course data obtained by CGE sequence.

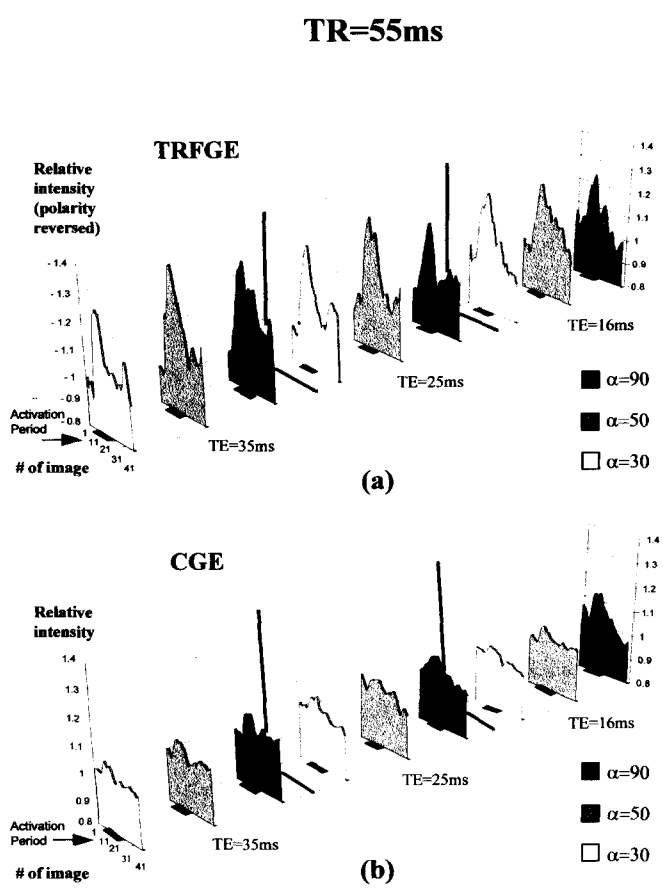


Fig. 5. (a) Another TRFGE time course data which were obtained by varying echo time TE from 16msec to 35msec and RF flip angle from 30° to 90° for a fixed TR(55msec). **(b)** Same as (a) but obtained by CGE technique.

7 sec was used for a single slice of 8mm thick which was located at the occipital pole near the calcarine tissue. In each experiment, 50 image sets were collected in series for time course study. First, image numbers from 1 to 10 were obtained at the rest state while stimulation was applied from image numbers from 11 to 20 by applying the visual stimulation, and again image numbers from 21 to 50 were obtained at rest state. Visual activation was applied by photic stimulation using 8Hz LED checker board.

Figure 4 shows the time course data of the signal change obtained using the TRFGE and CGE sequence with flip angles a ranging from 30° to 90° and repetition times of 35 msec, 55msec, and 65 msec in three steps, respectively. For this experiment, to examine the inflow effect, a relatively short echo time(TE=16msec) was used. As shown in Fig 4 (a), in the TRFGE time course data, nearly identical signal variation, independent of the RF flip angle a as well as repetition time TR, suggests that the signal variation is not affected by the in-flow effect(see Fig. 4(b) for comparison with CGE results) but probably due to the susceptibility effect. However, as shown in Fig. 4(b), in the CGE-time course data, the inflow effect is pronounced as flip angle increases and similar trend is also observed as the repetition time decreases. If, in fact, inflow effect is the dominant factor, these observations are expected in CGE sequence. On the other hand, in CGE sequence, increasing susceptibility effect should be observable as the flip angle decreases with increasing repetition time as well as echo time. This expected signal change observed in CGE was small even with relatively large TR and small a which be-

lieved to be of the susceptibility effect dominant, i.e., overall results appear small and signal to noise ratio found to be poor. Fig. 4(b) is a clear indication of the strong and dominant role of the inflow effect observed in CGE-fMRI.

In Fig. 5, another time course study data obtained by both TRFGE and CGE sequences with varying echo time TE are shown, namely TE of 16msec, 25msec, and 35msec, with varying flip angle a of 90°, 50°, and 30°. In an attempt to observe the susceptibility effect, a relatively large repetition time is used, i.e., TR=55msec. As shown in Fig. 5(a), again the results obtained by TRFGE sequence suggest that the susceptibility contrast in the TRFGE technique is independent of the TE as expected. However, the signal change observed could be in large part due to the susceptibility effect. As evidenced from the data, the overall signal decay is clearly visible as TE increases but remains relatively constant, suggesting that the susceptibility contrast is not as strongly affected as the inflow signal shown in Fig. 4(b). Therefore, the result of TRFGE sequence is clearly distinguishable from the conventional gradient echo sequence where decrease of the signal is observed with the increase of TE. In short, the TRFGE technique appears to be insensitive to the in-flow effect and the contrast developed seems mainly due to the susceptibility effect produced by the RF pulse rather than TE. This is confirmed in Fig. 5(a) where the signal is nearly independent of TE values. The result suggests that the "short echo time" can be used thereby one can eliminate the potential T2 signal decay. It should also be noted that the signal(time course) amplitude variation shown in Fig. 5(a). is quite different from that of the data obtained from CGE experiments with similar experimental conditions(see Fig. 5(b)). That is, the signal patterns in the case of TRFGE are not only insensitive to the various flow sensitive parameters but the time course signal decay is much more gradual suggesting that the signal variation is not flow but some form of oxygen metabolism occurring during the photic stimulation.

DISCUSSION AND CONCLUSIONS

Our results have demonstrated that conventionally employed gradient echo T2* imaging for the functional imaging is contaminated with a significant fraction of inflow effect of arterial blood which has no direct relation to the oxygenation process involved with external stimulations such as the photic and motor stimulations. The CGE technique clearly complicates the functional measurement by mixing the two independent processes, namely inflow effect of arterial blood and susceptibility effect, thereby making the observation of pure deoxygenation process more difficult. Although a number of investigations support the susceptibility dependent T2* effect based on the fact that change of TE often increases the corresponding susceptibility differences between stimulation and rest periods, many experiments have consistently shown that there could be other effects such as the inflow effect(12). We believe that the many inconsistencies found in those the fact that many similar experiments have led often to the quite different results. This can happen in experiments using the CGE technique since the method is indeed dependent on the region selected, that is, whether the selected region contains large arterial vessels or not.

On the other hand, as has been demonstrated and shown, using the tailored RF pulse sequence one can effectively measure the susceptibility contrast which is free from in-flow effects as well as backgrounds. Since the TRFGE sequence effectively suppress the signals from normal tissues which are considered to be not only nuisance but disturb the interpretation of data. In conclusion, it has been demonstrated that TRFGE technique is not only more sensitive to the susceptibility contrast but also insensitive to the other effects such as the in-flow effect and background signals. The latter eliminates the need of "background subtraction" usually necessary in the conventional fMRI. The TRFGE technique, therefore, could be a suitable method for the "susceptibility only" functional imaging, that is the measurement of the quantitative oxygenation and deoxygenation processes processing without the interferences from the in-flow effect and backgrounds.

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=국문초록=

Tailored RF 경사자계 영상법을 이용하여 혈류효과를 배제한 자화율효과만의 뇌기능 영상을 얻을 수 있었다. 일반적인 RF를 이용한 경사자계 뇌기능 영상법은 빠른 경사자계 영상법으로 인해 정맥뿐만 아니라 동맥에서의 혈류효과와 T2* 효과가 합쳐진 영상을 얻게되는 반면, tailored RF를 이용한 경사자계 영상법은 산소소모와 관계된 자화율 변화에 의한 뇌기능 영상을 얻을 수 있었다. 본 논문에서는 tailored RF를 이용하여 뇌기능 영상에서 자화율효과와 혈류효과를 명확히 구분할 수 있음을 보였다. 그리고 실험결과로 얻은 신호는 충분히 크고 산소 소모의 변화를 보다 더 정확히 표현하므로 지금까지 다른 경사자계 영상법으로는 어려웠던 뇌기능 영상에서 정량화된 산소 신진대사 연구의 가능성을 보여 주었다.