Fig. 4 "*Complementary Color Response* (CCR)"

Case A and Case B in **Table 3**. The data of **M-MHS** (●) from the 2nd MCV-Test when **CCR** (★ or ☆) reappeared in both subjects are plotted on the radar chart of Munsell 80-Hue Score.

Article Title:

Stepping Stone Sampling for Retrieving Artifact free-EEG during

Functional Magnetic Resonance Imaging

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Abstract

Ballistocardiogram and imaging artifact cause major interference with simultaneous EEG
and functional magnetic resonance imaging (fMRI) recording. In particular, the large
amplitude of the imaging artifact precludes easy retrieval of EEG signals during fMRI
scanning. Recording with 20000 Hz digitization rate combined with 3000 Hz low pass filter
revealed the real waveform of the imaging artifact, in which it was elucidated that each
artifact peak precisely corresponded to each gradient component, and actually had
differential waveforms of the original gradient pulses. Based on this finding, to retrieve EEG
signal during fMRI acquisition, a blip type echo planar sequence was modified so that EEG
sampling might be performed at every 1000 s (digitization rate 1000 Hz) exclusively in the
period in which the artifact resided around the baseline level. This method, called 'stepping
stone sampling' substantially attenuated the amplitude of the imaging artifact. The remnant
of the artifact was subtracted from the averaged artifact waveform. In human studies,
activity was successfully retrieved by inspection, and its attenuation/augmentation was
observed during eyes-open/closed periods. Fast Fourier transform analysis further revealed
that even from DC up to 120 Hz, retrieved EEG data during scanning had very similar power
distributions to the data during no-scanning, implying the availability of the high frequency
band of the retrieved EEG signals including even band.

INTRODUCTION

Positron emission CT (PET) and single photon emission CT (SPECT) have made it possible to map brain functional activities during various cognitive tasks in terms of brain metabolism and hemodynamics. These imaging techniques, however, cannot yet evaluate discrete neural correlates exclusively related to task execution because of their poor time resolution, and therefore their *task-relatedness* remains to be better defined. The advent of functional magnetic resonance imaging (fMRI) has improved the situation due to its fairly good temporal and anatomical resolution (Belliveau *et al.*, 1991). On the other hand, currently available electrophysiological tools of electroencephalogram (EEG) and magnetoencephalogram (MEG) facilitate evaluation of human cognitive activities with a time precision of milliseconds, far surpassing the above-mentioned imaging techniques. Therefore, parallel EEG recording with fMRI acquisition provides a statistical model of the time course changes of each EEG event applicable to the fMRI volume train, with which the neural correlate of the EEG event can be mapped onto the high-resolution brain tomographic/surface view. This methodology should find wide application ranging from neurophysiological to clinical investigations. However, simultaneous EEG/fMRI recording has been associated with some serious problems, among which the most critical are two artifacts manifest on the EEG. The first of these is the cardiac-related artifact whose amplitude is up to around 200 ☐V that emerges in synchronization with the cardiac pulse (Allen *et al.*, 1998). Two possible causes of this artifact have been proposed: an electromotive force (Faraday's law) and a blood flow effect (Allen *et al.*, 1998). Several methods have been devised to reduce this artifact such as use of a spatial filter (Bonmassar *et al.*, 1999), and average subtraction (Allen *et al.*, 1998). We substantially reduced the amplitude of this artifact to an acceptable level in many cases by employing a vacuum cushion system that could fix subject's head and conform to the individual head shape (Anami *et al.*, 2002). Based on the fact that appropriate suppression of head micro-vibration can laregely remove the artifact, we thought that the more significant cause of this artifact was electromotive force. This artifact was called ballistocardiogram. These solutions have enabled interleaving recording wherein

EEG recording and fMRI scanning are performed alternatively. Several studies to date on

controllable EEG phenomena such as visual evoked potentials (VEPs) (Bonmassar *et al.*, 1999;

Kruggel *et al.*, 2000; Bonmassar *et al.*, 2001) and event-related potentials (ERPs) (Kruggel *et al.*,

2001) were conducted using interleaving recording. Many studies have also focused on spike

mapping for epilepsy using spike-triggered fMRI (Warach *et al.*, 1996; Krakow *et al.*, 1999;

Lazeyras *et al.*, 2000; Lemieux *et al.*, 2001a). However, epileptic spikes, a typical spontaneous EEG

phenomenon cannot be completely captured by interleaving recording.

Second, the imaging artifact in the middle of fMRI acquisition, which has an overwhelmingly

spiky waveform, is generated in association with fMRI scanning (Allen *et al.*, 2000; Hoffmann *et*

al., 2000). This artifact markedly interferes with continuous EEG recording during fMRI

acquisition. But the necessity of continuous EEG recording to fully observe spontaneous EEG

phenomena such as epileptic abnormalities has prompted some laboratories to address this problem,

with partial success, (Hoffmann *et al.*, 2000; Goldman *et al.*, 2000; Allen *et al.*, 2000), and with

actual application to epilepsy (Lemieux *et al.*, 2001b; Salek Haddadi *et al.*, 2002). However,

acquisition of EEGs comparable to ones recorded in a clinical EEG laboratory is not yet feasible

because of the inherent constraints resulting in the frequency dips in multiples of 0.61 Hz and 7.36

Hz (Hoffmann *et al.*, 2000), or limited frequency range up to 40 to 50Hz (Allen *et al.*, 2000;

Hoffmann *et al.*, 2000). In particular, recording EEG phenomena of very low amplitude during

fMRI acquisition with sufficient quality for objective evaluation is difficult. This is, for example,

reflected by the estimation that 2 or 3 times of the averaging number was required to observe ERPs

(Kruggel *et al.*, 2001).

Given these circumstances, based on the notion that the imaging artifact from the MRI scanner

on EEG must have a very different nature from EEG, a typical biological signal, especially in terms

of its frequency and amplitude, we observed this artifact with a 20000 Hz digitization rate and 3000

Hz low-pass filter (LPF), and revealed its detailed characteristics. Based on this observation, we

devised a new approach to attenuate the artifact amplitude and retrieve a high quality EEG signal in

the middle of fMRI acquisition. Here we report our initial results from continuous EEG recording with fMRI acquisition, which make available a wider frequency range.

BASIC CONCEPTS FOR ATTENUATING IMAGING ARTIFACT

Ballistocardiogram

Ballistocardiogram is an induced current based on Faraday's law, which is caused by ballistic head movement due to cardiac pulsation. We proposed a simple method to suppress the artifact by immobilizing the head with a vacuum cushion system, which was described elsewhere (Anami *et al.*, 2002). We adopted this approach in the present study too.

Imaging Artifact

Usually we observe low-pass filtered waveforms of imaging artifacts, e.g., with a DC range up to 100 Hz under a common EEG setup. However, as the artifact is the consequence of sequential RF and gradient pulses working in □ s time scale, the original artifact must consist of components with a much higher frequency than those of EEG. To obtain the real waveform of the artifact, we recorded it with 3000 Hz LPF combined with a digitization rate of 20000 Hz, which eventually enabled observation of the complete waveform of the imaging artifact.

An example of an artifact waveform obtained from a typical blip type fMRI sequence, EPIS sequence (Siemens: ep2d_fid_60b2080_62_64.ekc) is illustrated in Fig.1. By collating each component of the artifact waveform with the fMRI sequence, it was elucidated that 1) the artifact had complicated but consistent waveforms, and each peak component corresponded precisely to an RF or a gradient pulse, which implies that RF and gradient pulse are major causes of the imaging artifact. 2) The artifacts by gradient pulses (10^3 to 10^4 □V) are much larger than those by RF pulses (up to 10^2 □V) in amplitude, and thus the gradient artifact makes up almost all of the imaging artifact (Fig. 1B: a, b, 1C: a', b') This result is consistent with that of Hoffmann *et al.*, 2000. The outstanding frequency of the underlying imaging artifact is that of the readout

gradient artifact, 833 Hz (period of the readout gradient: 1200 □s) that is, however, out of the

EEG frequency range and not observable. The observable frequencies within the EEG band were

defined by loops of an fMRI sequence that resulted in serious artifacts within the EEG band

(Hoffmann *et al.*, 2000). Although an RF emission of 64 MHz resonance frequency is definitely

outside a bioamplifier's frequency range, it can cause small artifacts on the EEG record (Fig.1C:

a', b') (Hoffmann *et al.*, 2000). This seems to be attributable to the fact that the induced current

caused by high RF power based on electromagnetic or electrostatic coupling is easily transformed

by a demodulation effect in the non-linear parts in the hardware system into the low frequency

artifact within an EEG amplifier's frequency range and results in artifacts on the EEG record. 3)

An artifact component caused by one gradient pulse consisted of a pair of peaks, one of which

deflected positively or negatively, and the other inversely (Fig.1B: c, d, 1C: c', d'). This finding

supports the contention that gradient artifact is mainly due to electromagnetic coupling

(Faraday's law) (Allen *et al.*, 2000; Hoffmann *et al.*, 2000), and thus the artifact from one

gradient pulse, in principal, has the differential waveform of the corresponding gradient pulse.

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Fig.1 around here

Imaging artifact waveform on EEG record from one slice scan

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These observations imply that we can predict and control the waveform and time schedule of the

artifact. Based on this concept, in order to attenuate the large amplitude of the gradient artifact, we

devised a strategy in which when EEG sampling and fMRI scanning are completely synchronized,

the differential waveforms of gradient pulses periodically made artifact-free interspaces that

allowed EEG sampling with a high signal-to-artifact ratio. Here, this method was called the

'stepping stone sampling method' (SSS). After recording the artifacts with SSS, recorded raw data

still have residual artifacts, which are subtracted from the averaged artifact to retrieve the EEG signal.

METHODS

Subjects and Materials

For the phantom study, a bottle type phantom (. = 12 cm) filled with cupric sulfate solution was employed. For the human study, five healthy subjects were recruited (two males and three females, average age 32 y.o.). All five subjects participated in the EEG/fMRI experiment, and one of the female subjects also participated in the fMRI experiment. All subjects provided written informed consent, and the study was approved by the ethics committee of the National Center Hospital for Mental, Nervous, and Muscular Disorders, National Center of Neurology and Psychiatry.

General Description of Stepping Stone Sampling

Electrode and Cable

Ag-AgCl electrodes attached to metal leads composed of 99.96% copper and 0.04% oxygen were prepared for the fMRI environment; not only the cables but also the electrode plate were shielded. An electrode plate has another Ag plate that was placed over it with an insulated layer in between, and which was connected to the grounding lead (Fig. 2B). The Cz electrode for common reference had as many cables as the number of active electrodes needed to make a twisted pair cable for each of them (Star-burst electrode). Ag-AgCl electrodes were applied to F3, F4, C3, Cz (reference), C4, Pz, O1, O2, A1, A2 according to the international standard 10-20 system (Fig. 2A). All electrodes were mounted on a custom-made electrode cap. Note that signals from A1 and A2 positioned at bilateral mastoid positions respectively, referred to Cz site were recorded as active electrodes. To minimize the distance between the active electrodes and the referential one, all leads first went up to the Cz site, and all of which were twisted with one of the Cz leads, and grouped together so that

they form one bundle.

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Fig.2 around here

Electrode placement and structure

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The bunch of cables was carried straight outside the magnet, and the cables went out of the magnet

room to be connected to an RF filter. Outside the magnet room, the cables from the RF filter were

connected to the head box of the EEG bioamplifier that was electrically floated. EEG was recorded

referring to the Cz site.

fMRI Sequence Programming and Acquisition

To achieve the SSS method, the EPIS sequence (the details in Fig.1A, and 1B) was modified by

removing the first spoiler, changing the time schedule (ramp up/down and duration) and

amplitude of gradient pulses and RFs, and changing the sampling time as well. The artifact by RF

pulses was found to be much smaller than that by gradient pulses under our fMRI equipment; the

former had some hundred □V, while the latter had a few thousand □V. This finding allowed us

to focus on circumventing the artifacts by gradient pulses, ignoring those by RF pulses. Large

artifacts are engendered by electromagnetic coupling and assume the same differential waveform

as that of the original gradient pulse, with an upward change (ramp up) resulting in a positive

peak and a downward one (ramp down) in a negative one. In contrast, when there is a gradient

plateau with no such changes, even when the gradient coil is on, in the absence of changes (no

ramp up/down), no artifact is produced. However, preliminary experiments revealed that the true,

observed results were different from theoretical considerations in the following respects. First, at

every transitional point of a gradient pulse from ramp up/down to plateau, or from plateau to

ramp down/up, the artifact actually had a slower return to the baseline level than the predicted

differential waveform. In fact, it took 600 □s to recover to the baseline level from a peak top.

Second, in some cases, in the interval set between a pair of neighboring artifact peaks during

which the gradient pulse was on, artifact did not completely return to the baseline level. Instead it

preserved a constant value of some hundred □V, probably because this kind of artifact was

caused by electrostatic coupling which under the small stray capacitance had basically a

proportional relationship to the gradient pulse waveform. Based on these principles and the actual

observations, a new sequence was programmed with a PARGEN (Siemens) compiler so that

differential waveforms of the gradient pulses in the sequence had almost artifact-free interspaces

at every 1000 □s interval among the artifact peaks, which allowed the EEG to be sampled

consistently within those clear interspaces with a 1000 Hz digitization rate (Fig.3A, 3B).

Each gradient pulse component was arranged in the above way. In particular, to realize stable and

appropriate EEG sampling in the series of readout gradient artifacts, 400 □s still time was added

at every peak-top of the sine wave gradient pulses. This provided a near-baseline interspace by

differential procedure (Faraday's law), 'a sampling shelf' that was long enough for EEG to be

digitally sampled in a resultant readout gradient artifact. (Fig 3D.) This sequence was called

'stepping stone sequence'. Fig.3A and 3B showed that EEG sampling points at 1000 Hz

digitization rate drop in baseline interspaces on the differential gradient waveform of the stepping

stone sequence all the time. The details of the timing table and the parameters of the sequence

were listed in Fig.3A, 3C, and 3D.The bandwidth of the readout gradient was 1136 Hz. The

position of an electrode and a related circuit defines polarity (positive or negative) and the

amplitude of individual imaging artifacts on the EEG record, leading to a variety of artifact

waveforms across the multiple channels. However, the fact that the time schedule of gradient

ramp up/down is the same across the channels in combination with the Sample / Hold mechanism

of the EEG amplifier assures phase-locked EEG sampling across the channels, with the stepping

stone sampling working across the multiple channels.

As described above, the actually recorded artifact is, however, somewhat different from the theoretical prediction. Slow recovery to the baseline level can be treated by putting additional time-shift in a sequence, but the problem of persisting potential hanging over the baseline is difficult to solve perfectly, which results in high frequency artifacts. Most of these can be filtered out by LPF, but low amplitude artifacts persist on the data. This requires an additional post hoc artifact correction procedure.

fMRI acquisition was conducted on a 1.5T MRI scanner with a circular polarization coil (Siemens Magnetom Vision Plus, Siemens, Erlangen, Germany). Acquisition was manually started, which also immediately initiated EEG sampling via a trigger sent from the MRI scanner.

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Fig.3 around here

Schematic diagrams of the stepping stone sequence

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EEG Acquisition

For EEG recording, a digital amplifier, 32ch. SynAmps (Neuroscan Lab, Sterling, VA USA) controlled by SCAN4.2.1 program installed in a PC (Pentium III 600MHz) was employed. EEG data were sampled at a 1000 Hz digitization rate and with 0.336 $\square$V/bit amplitude resolution and a dynamic range of 22 mV. According to our experiments, 1 $\square$s shift of EEG sampling sometimes made a 70 $\square$V difference in the underlying imaging artifact during the readout gradient. This fact implied that for phase-locked sampling EEG data within near-baseline interspaces, almost $\square$s order precision and temporal consistency in synchronization of EEG data sampling together with gradient pulse firing would be required. Accordingly, we adopted a single clock driving of the whole EEG/MRI system by driving SynAmps with the MRI scanner's clock, which assured good phase-locked EEG sampling. For performing external Sample/Hold in SynAmps, Neuroscan's

standard procedure was completed (see http://www.neuro.com/ext_sh.htm). For modifying too high

frequency of the MRI scanner's internal clock (4 MHz) to the acceptable frequencies for SynAmps

driving, a clock divider, CD-2 (Physio-Tech, Tokyo, Japan) was used, which down sampled the

original frequency to provide several clock frequency options (1000 Hz, 2000 Hz, 10000 Hz, 20000

Hz) to drive the SynAmps. The data were sampled at a 1000 Hz digitization rate with 10000 Hz of

the external clock provided by CD-2, and had 2000 Hz of the upper cut-off frequency of the

anti-aliasing filter.

The very high cut-off frequency makes the imaging artifacts sharp and high with a narrow width,

which on the other hand, provides wide near-baseline interspaces among artifact spikes that make

sampling at the near-baseline interspaces much easier. However, this recording condition can cause

aliasing contaminations on the EEG record, although in practice aliasing does not cause a major

problem, as is further discussed in the APPENDIX.

The first EEG sampling point on fMRI sequence at the start of simultaneous recording fixes the

phase-locked point and determines how high the amplitude of the imaging artifact remains in the

rest of the underlying recording. This implies that accurate alignment of the starting point of the

fMRI scanning and EEG sampling is necessary.   For this purpose, a trigger from the MRI scanner

embedded at the head of the fMRI sequence was sent to the SynAmps to initiate data sampling. If

necessary, an additional detailed adjustment could be performed in the clock divider that allowed

modification of the sampling starting point with 0.125 $\square$s interval.

EEG Post-processing

All EEG signal processing was implemented on Matlab (Mathworks Inc., Mass, U.S.A Residual

artifact was subtracted from the averaged-artifact template. Every subtraction point is determined

precisely by TR, because the EEG amplifier was driven by the MRI scanner's clock. 100ms span of

data prior to the first point of, and whole data of one volume scan, and following data of next 300

ms were grouped together and averaged across all volumes to make an averaged-artifact template.

50 ms of data prior to the starting point were used to determine the baseline level. The template was

eventually subtracted from every artifact on data for each channel basis. Following the subtraction,

the data of all channels were filtered out by elliptic LPF. If necessary, the reference can be changed.

For mastoid reference, from raw data, (AR - Cz), (AL – Cz), (A1 - Cz), (A2 - Cz),

(AL –Cz) – (A1 – Cz) = AL – A1,

(AR –Cz) – (A2 – Cz) = AR – A2

where AR denotes an active electrode on right scalp, and AL one on left scalp.

Similarly for linked mastoid reference

(AR – Cz) – (1/2)*{(A1- Cz) + (A2 - Cz)} = AR – (1/2)*(A1+A2)

Notes on Individual Experiments

The experiments in this study are subdivided into three parts: a stepping stone sequence validation

experiment, an experiment with a phantom, and one with a human for EEG/fMRI.

Validation of the Stepping Stone Sequence

To verify if the stepping stone sequence is sufficiently sensitive for BOLD contrast, we compared

fMRI activation by the stepping stone sequence with that by EPIS sequence (Siemens:

ep2d_fid_60b2080_62_64.ekc) using a visual stimulation paradigm without simultaneous EEG

monitoring. EPIS sequence is a FID type (gradient echo type) sequence (64 matrix, readout

bandwidth 2080Hz), featuring fast image acquisition with mosaic image format. This sequence is

composed of spoiler - fat -sat pulses (1-3-3-1 pulses) - spoiler - slice selection pulse - dephasing and

rephasing pulses - readout pulse – spoiler in this order (Fig.1A,1B). One subject was recruited for

this experiment. Two sessions were performed on different days with a week interval for the

test-retest experiment. Checkerboard visual stimulation (8Hz, 8*8 matrix) was employed for task

blocks, and hair-line cross fixation for control blocks. Stimuli were displayed on the screen from an

LCD projector, introduced into the MRI gantry and presented to the subject via a mirror mounted on

the head coil. One block had 10 volume scans, and one run consisted of 10 blocks that were

preceded by 10 dummy scans. Task and control had 5 blocks respectively. Functional images were collected in two runs: one with EPIS sequence (TR = 3000 ms, TE = 60ms, flip angle = 90 degree, FOV: 192 mm, 64*64 image matrix) and the other with Stepping Stone Sequence (TR = 3000 ms TE = 60 ms flip angle = 90 degree, FOV: 192 mm, 64*64 image matrix). From each of the runs, 100 sets of 20 slices, 6 mm thick axial images with 0.6 mm gap in between parallel to the anterior-posterior commissure plane covering the whole brain were acquired. Data analysis was performed with SPM99 (Wellcome Department of Cognitive Neurology, London, UK). fMRI data were treated with realignment and smoothing with Gaussian kernel with 8Hz FWHM, after which statistical analysis was performed using a general linear model, with statistical significance defined as corrected $p < 0.05$. The global maximum point was obtained on the statistical result. Separately, the smoothed Analyse format image files (not realigned) were read in on Matlab for the following procedures. Then, in the vicinity of the global maximum point, the ROI with a dimension of 9 mm (3 voxels on x axis) * 9 mm (3 voxels on y axis) * 6 mm (1 voxel on z axis) showing the maximum percent change in the NMR signal between the task and the control blocks was detected in each run. The S/N ratio was obtained from the signal of an ROI in white matter (signal value) and that in an empty space near the upper right edge (noise value) of the image matrix.

EEG/fMRI Experiment with a Phantom

In order to estimate to what extent the amplitude of imaging artifact is reduced by the SSS method and how the smaller artifact acquired with it facilitates retrieval of the EEG signal from among various imaging artifacts, imaging artifacts on one channel of the EEG record were compared between the SSS and non-SSS methods with the stepping stone sequence and one clock driving but without start alignment wherein stepping stone sampling did not work, but artifacts with similar characteristics could be obtained. The phantom surface was coated with EEG paste to create an electrical circuit composed of active, referential and ground electrodes. The circuit

extended half way round the bottle, whose aperture area was approximately 55 cm^2 set vertically

to the z axis direction in the magnetic field. Impedance was adjusted to less than 1kΩ. 40 volume

scans were recorded in both of these two sessions. Data were filtered with 100Hz LPF, and each

artifact was subtracted from the averaged artifact that was averaged across the last 25 volume

artifacts.

EEG/fMRI Experiment with a Human Subject

Continuous EEG/fMRI was recorded with five human subjects. 100 volumes each consisting of 20

axial slices (5mm thickness, no gap; TE: 40 ms; TR: 3000 ms; FOV: 192 mm; 64*64 image

matrix) were acquired using the SSS method. To suppress the ballistocardiogram, the vacuum

head fixation system (Med-Tec Co., USA) was employed. In the inflated (soft) condition, it can

mould to the subject's head shape. Once it is deflated, it becomes solid but continues to retain the

subject's head's shape precisely, and thus can immobilize the head in a comfortable position.

Unlike the soft and elastic cushions or puddings usually used in fMRI experiments for head

fixation, the solidity and close contact with the whole head achieved with this system effectively

suppress the head's micro-vibrations leading to substantial attenuation of the ballistocardiogram

to an acceptable level. Actually the plastic bag pillow filled with small plastic particles was set to

fill in the clearance gap between the subject's head and the head coil. Next, the air in the pillow

was deflated so that the subject's head was properly fixed and comfortably supported in the head

coil. Deflation was adjusted to suppress the head's micro-vibration by observing the

ballistocardiogram on the EEG. Impedance at all electrodes was preserved at less than 10kΩ.

RESULTS

Validation of the Stepping Stone Sequence

The SPM{T} showed the activations in the bilateral occipital areas in both results with the stepping

stone sequence and the EPIS sequence with the checkerboard stimulation paradigm(Fig.4). The time

course of the ROI showing the maximal percent signal change between the task/control blocks with the two sequences were also demonstrated in Fig.4.

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Fig.4 around here

Activated areas in the occipital lobe and time course NMR signal changes

obtained by the two fMRI sequences

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The result of the maximal percent change in the NMR signal between the task/control blocks and S/N ratio was shown in Table.1. Percent change was better with EPIS sequence, while S/N ratio was better with the stepping stone sequence.

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Table.1. around here

Percent change of the NMR signal and S/N ratio of EPIS and Stepping Stone sequence

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EEG/fMRI Experiment with the Phantom

Fig.5A demonstrated the artifact waveform from SSS and non-SSS acquisition. Averaged peak-to-peak amplitude of the imaging artifact from one volume SSS acquisition was $83.9 \pm 1.4 \Box V$, while non-SSS was $1910.5 \pm 28.0 \Box V$. Fig.5B illustrated the data from non-SSS, SSS, and background noise respectively after artifact correction. The data from non-SSS still had remaining artifacts whose frequency was slightly more than 10 Hz. In fact, the stepping stone sequence with 40 ms of TE requires 92 ms for one slice scan, leading to 10.87Hz periodicity for multi-slice scan in consequence, which was reflected by the frequency of the residual artifact on non-SSS data. In

contrast, SSS appeared to have no observable residue arising from the imaging artifact, but the

amplitude of the noise in SSS looked smaller than the background noise. The spectrograms in

Fig.5C revealed that the background data had a greater amount of 50Hz hum noise than those of

SSS. Accordingly the underlying amplitude difference is probably caused by the phenomenon that

50Hz hum noise often happened to be phase-locked with the MR scanner's internal clock, with

subtraction correction often attenuating hum noise as well leading to less residual noise in SSS than

background noise.

The spectrograms also show that imaging artifact existed over almost all frequency ranges. In

non-SSS acquisition, although the result of subtraction in the high frequency band appeared to be

successful in this case, there were still some residual artifact powers observable at lower

frequencies less than 12Hz. In contrast, subtracted data from SSS acquisition were very similar to

those from background noise, assuring that almost all imaging artifacts were successfully removed.

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Fig.5 around here

Imaging artifacts recorded by SSS and non-SSS sequences on phantom study

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EEG/fMRI Experiment with Human Subjects

The EEG data were acquired from continuous EEG/fMRI recording with SSS method. The acquired

data were treated with LPF (100 Hz). Table.2 showed the averaged amplitude of remnants of

imaging artifact across the seven channels (F3 – Cz, F4 – Cz, C3 – Cz, C4 – Cz, Pz – Cz, O1 – Cz,

O2 – Cz) and the retrieved □activity on O2 during fMRI acquisition after artifact correction for

each subject. □ activities recorded outside the magnet were also demonstrated for comparison with

that during fMRI acquisition. All averaged artifact amplitudes were less than 165 □V which was

approximately 1/10 of a common artifact amplitude in EEG recording during fMRI acquisition.

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Table. 1 around here

Statistics of Alpha activity outside magnet and during fMRI acquisition

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Fig.6 showed the actual time domain EEG data on O2 site for 10 s after artifact correction. Attenuation/augmentation of □ activity was observable during the eyes open/closed period respectively

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Fig.6 around here

Artifact-corrected EEG record during fMRI acquisition

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Temporal FFT analysis on EEG signal was performed on Matlab throughout 100 volume scans (5 min). A subject was instructed beforehand to open/close his eyes spontaneously at every two volume scan interval. Fig.7 demonstrates the result on O2 site. For reference, the first 15 scans did not have any artifact correction. During this period, imaging artifacts were displayed as periodical sharp bands over most frequency ranges. During the last 85 scans (from the end of the imaging artifact until 300 s), the power augmentation/attenuation of □ activity according to the eyes opened/closed periods were clearly visible. The FFT profile from DC up to 120 Hz during the last 85 scans was very similar to the profile without scanning (from 300 s until the end of the record).

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Fig.7 around here

Spectrogram of artifact-corrected EEG during fMRI acquisition

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DISCUSSION

Imaging artifacts from echo-planar sequence differ markedly from biological signals in terms of their frequency and amplitude. The very high digitization rate and high cut-off frequency in LPF revealed its real waveform and elucidated that the artifact precisely traced the components of the echo-planar sequence. Due to the fiercely deflecting waveform, even a small shift in data sampling can change the consequent artifact waveform. Artifacts cannot be precisely subtracted with averaged artifacts, unless each scan has a very similar waveform. We solved this problem with the one-clock driving that controlled the whole EEG/fMRI system, and with the start alignment of EEG sampling and fMRI sequence using trigger starting.

The artifact observation also revealed that the real amplitude of the artifact could be 40 mV in our MRI equipment, which seems to be in concordance with a theoretical calculation at 2 Tesla (Allen *et al.*, 2000). This high voltage leads to potential data overflow out of the amplifier dynamic range. However, such a low cut-off frequency in LPF as widely used in clinical EEG examinations strongly attenuates and smoothes the high frequency artifact, and thus, critically, LPF may conceal the artifact clipping and result in apparently misleading data. Allen *et al.* (2000) solved the overflow problem by putting a 70Hz LPF following a small gain differential amplification, which can substantially attenuate the artifact's amplitude to keep it within the amplifier's dynamic range. The SSS method can be an alternative solution, which is, in principle, irrespective of the amplifier's dynamic range, because the sampling is performed exclusively within the periods in which the signal resides around the baseline. In other words, regardless of the height of the original artifact amplitude, data can be obtained consistently within the amplifier's dynamic range. According to the result of the phantom experiment described above, the small artifact amplitude contributes to less residual imaging artifact on EEG data after artifact correction. Furthermore, the irrelevancy to

artifact amplitude permits a large amplifier gain that has a higher amplitude resolution, which is important especially to estimate low amplitude EEG phenomena such as ERPs.

The SSS method had a substantial effect on attenuating the imaging artifact amplitude. Actually it attenuated the artifact amplitude to less than 1/22 of the original one in the present phantom experiment. This effect actually contributed to the precision in the averaged-artifact subtraction procedure, which is important because multiple slice scans in which a single slice scan requires 80 to 100ms for acquisition commonly result in large peak artifacts of 10 to 12Hz in frequency, so that the residues due to such incomplete artifact subtraction also have a similar frequency, thereby sometimes mimicking □ activity on human EEG records. According to our experiments, 1 □s shift of EEG sampling sometimes makes a 70 □ volt difference in the underlying imaging artifact during the readout gradient. Hence the sampling shelf assures stable EEG sampling exclusively during near-baseline among the fiercely fluctuating artifact spikes caused by the readout gradient. On the other hand, the sampling shelf broadens the read out gradient span (64 ms), which can give rise to disadvantages with the SSS method; 1) possibility to distort BOLD contrast images especially in basal forebrain, 2) a longer acquisition time for an fMRI run, 3) slightly lower percent signal change between the task/control blocks. To compensate for these disadvantages, rather short TE should be used for SSS method. On the other hand, the narrow bandwidth contributes to good S/N ratio on fMRI images and low amplitude of imaging artifact on EEG record contributes to good quality EEG.

To sample EEG data within the sampling shelves together with 1000Hz digitization rate, the combination of 300 □s ramp up – 400 □s still time – 300 □s ramp down in readout gradient pulses is required using the Siemens Vision Plus scanner. However this combination constraint can be improved by high-speed gradient capability and more digitization rate options in an EEG amplifier. That is, the faster gradient speed in combination with an appropriate digitization rate facilitates the shorter readout gradient span leading to a shorter fMRI acquisition time and no concern about potential image distortion. For example, 200 □s – 225 □s – 200 □s in combination with a 1600Hz