Steady-state BOLD Response to Higher-order Cognition Modulates Low-Frequency Neural Oscillations

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Abstract

■ Steady-state responses (SSRs) reflect the synchronous neural oscillations evoked by noninvasive and consistently repeated stimuli at the fundamental or harmonic frequencies. The steady-state evoked potentials (SSEPs; the representative form of the SSRs) have been widely used in the cognitive and clinical neurosciences and brain–computer interface research. However, the steady-state evoked potentials have limitations in examining high-frequency neural oscillations and basic cognition. In addition, synchronous neural oscillations in the low frequency range (<1 Hz) and in higher-order cognition have received a little attention. Therefore, we examined the SSRs in the low frequency range using a new index, the steady-state

BOLD responses (SSBRs) evoked by semantic stimuli. Our results revealed that the significant SSBRs were induced at the fundamental frequency of stimuli and the first harmonic in task-related regions, suggesting the enhanced variability of neural oscillations entrained by exogenous stimuli. The SSBRs were independent of neurovascular coupling and characterized by sensorimotor bias, an indication of regional-dependent neuroplasticity. Furthermore, the amplitude of SSBRs may predict behavioral performance and show the psychophysiological relevance. Our findings provide valuable insights into the understanding of the SSRs evoked by higher-order cognition and how the SSRs modulate low-frequency neural oscillations.

INTRODUCTION

Steady-state responses (SSRs) refer to the periodic brain response evoked by noninvasive, regularly repeated stimuli. This form of response is based on the synchronous neural oscillations that are the intrinsic characteristics of neural activities and the basis of cognitive processes (Calderone, Lakatos, Butler, & Castellanos, 2014; Uhlhaas & Singer, 2010; Ward, 2003). The SSRs have been widely used in cognitive and clinical neurosciences and braincomputer interface research (Vialatte, Maurice, Dauwels, & Cichocki, 2010). A considerable amount of evidence support the proposal that SSRs may index the neural activities or brain activations, such as those observed in the ERPs (Wang et al., 2014; Thut, Miniussi, & Gross, 2012; Vialatte et al., 2010).

The steady-state evoked potential (SSEP) is one of the well-investigated forms of SSRs. The SSEP has a high signal-to-noise ratio and a stable amplitude over time and is sensitive to sensory stimuli (Gray, Kemp, Silberstein, & Nathan, 2003; Regan, 1989). Because of these significant advantages, the SSEP is extremely useful in examining basic cognition such as visual attention (Morgan, Hansen, & Hillyard, 1996), working memory (Ellis, Silberstein, &

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Nathan, 2006), neurological disorders (Uhlhaas & Singer, 2006; Krishnan et al., 2005), and other sensation processes (Nangini, Ross, Tam, & Graham, 2006; Plourde, 2006). However, it is difficult to examine low-frequency neural oscillations and higher-order cognition with SSEPs because of the required high frequency of stimuli presentation (Zhang, Xu, Huang, Cheng, & Yao, 2013; Regan, 1989).

Contrary to the electrophysiological techniques, the fMRI technique possesses high spatial resolution and lowfrequency signal fluctuations that allow investigation of the low-frequency neural oscillations in particular regions. In a previous study, we observed low-frequency steady-state BOLD responses (SSBRs) in the visual, senorimotor, and cognitive control regions in a simple RT task (Wang et al., 2014). The SSBRs were induced in task-related brain regions and reflected low-frequency neural oscillations that are independent of neurovascular coupling (Wang et al., 2014; Baria, Baliki, Parrish, & Apkarian, 2011). Therefore, the SSBRs expanded the scope of SSRs to slow (<1 Hz) and infraslow (<0.1 Hz) frequency bands and provided a direct means to investigate task-related low-frequency neural oscillations compared with brain activation, which strongly depends on neurovascular coupling. Given that the low-frequency oscillations occupy most of the brain energy consumption and play important roles in brain activities (Guerra-Carrillo, Mackey, & Bunge, 2014; He, 2014; Palva & Palva, 2012; Raichle, 2006), the SSBRs could be powerful in revealing mechanisms of brain functions.

Journal of Cognitive Neuroscience 27:12, pp. 2406–2415 doi:10.1162/jocn_a_00864

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It is worth noting that both SSBRs and SSEPs have been examined in sensory or perceptual tasks. Studies about SSEPs have rarely paid attention to higher-order cognition because we cannot accomplish complex tasks when stimuli are presented in a high frequency (e.g., alpha, beta, or gamma band). In contrast, the low-frequency BOLD signal fluctuations enable fMRI to detect higherorder cognition with the stimuli presentation rate of <1 Hz. The aim of this study was therefore to investigate higher-order cognition (e.g., semantic comprehension) from the perspective of low-frequency neural oscillations with the fMRI technique.

We hypothesized that low-frequency SSBRs could be evoked by higher-order cognition and could reflect underlying neural oscillations. First, we have demonstrated that SSBRs can be evoked not only in sensory and motor regions but also in cognitive control areas (Wang et al., 2014). Moreover, visual SSEPs can be observed to appear in the visual cortex (VC) as well as in the frontoparietal region (Vialatte et al., 2010). These findings indicate that regions for higherorder cognition also possess the characteristics of SSR. Second, in the infraslow frequency range, the BOLD signal fluctuations have been associated with electrophysiological signals (Hiltunen et al., 2014; Thompson et al., 2014; Pan, Thompson, Magnuson, Jaeger, & Keilholz, 2013; Vanhatalo et al., 2004) and behavioral fluctuations (Hiltunen et al., 2014; Palva & Palva, 2012; Thut et al., 2012; Monto, Palva, Voipio, & Palva, 2008; Leopold, Murayama, & Logothetis, 2003) and have been widely studied in resting states (Zang et al., 2007; Vanhatalo et al., 2004; Biswal, Zerrin Yetkin, Haughton, & Hyde, 1995). These studies suggest the physiological significance of low-frequency BOLD fluctuations. Furthermore, the recently developed method of blind hemodynamic response function (HRF) deconvolution allows us to obtain the neural level signals from BOLD level signals, eliminating interference from neurovascular coupling (Wu, Liao, et al., 2013; Glover, 1999). Using this method, we have demonstrated that SSBRs can reflect low-frequency neural oscillations. These progresses enable fMRI to uncover the mechanisms of higher-order cognition from the view of low-frequency neural oscillations.

METHODS

Participants and Procedure

Fifty-five young men, aged 18–20 years (mean \pm *SD* = 18.44 \pm 0.57 years), with normal or corrected-to-normal vision, participated in the experiment. All participants were right-handed (determined by the Chinese version of the Edinburgh Handedness Questionnaire, coefficients > 60; Wang et al., 2013), and free from any medication and neurological or psychiatric disorders. Written informed consent, approved by the research ethical committee, was obtained from each participant.

Each participant was asked to complete a semantic comprehension task in three blocks of 40 sentences.

Each of the 120 sentences contained 13 words with complete subject-verb-object structure (e.g., in Chinese: "我希望为我的家庭而努力学习"; in English: I want to study hard for my family; "我希望自己的生命能永不终结"; I hope my life can never come to an end). Each sentence was presented for 7 sec, plus a 1-sec prefixation and a 4-sec postfixation. Each block lasted for 8 min 20 sec with 8-min task (40 sentences × 12 sec) and 20-sec buffering. Participants were asked to judge whether the event in each sentence is possible and press a key with the left (impossible) or right (possible) thumb within 7 sec after the presentation of the sentence. This task required semantic comprehension, enabling us to study neural activities related to this cognitive process.

Data Acquisition

MRI data were acquired by a 3-T GE 750 scanner (General Electric Medical Systems, Waukesha, WI) equipped with high-speed gradients. A prototype quadrature birdcage head coil fitted with foam padding was applied to minimize head motion. In the block to acquire resting state activity (8 min 20 sec, 250 volumes), participants were required to remain motionless, fixate on a cross-hair, stay awake, and not think of anything in particular. Three task blocks were serially arranged about 5 min after the block for resting state with about 5 min interblock intervals. All functional images were acquired using an EPI sequence. Parameters were as follows: repetition time/echo time = 2000/30 msec, 39 slices, 64×64 matrix, 90° flip angle, 24-cm field of view, 4-mm slice thickness without gap.

Data Preprocessing

Functional images were preprocessed with the Data Processing Assistant for Resting-state fMRI (DPARSF 2.2, restfmri.net/forum/DPARSF; Yan & Zang, 2010). The first 10 volumes were discarded to ensure signal equilibrium and for the participants to familiarize themselves with the scanning environment. Another 12 volumes (two trials) were excluded to allow evoked fluctuations to appear. The remaining 228 consecutive images were slice-time corrected, spatially aligned, and spatially normalized to the Montreal Neurological Institute space using the standard SPM8 EPI template and resampling to 3-mm cubic voxels. Three participants were excluded from analysis because of large head motion (translation > 2 mm or rotation $> 2^{\circ}$). Two participants were excluded because they slept during scanning. For the remaining participants, there were no significant differences of frame-wise displacement (Power, Barnes, Snyder, Schlaggar, & Petersen, 2012) among the four blocks (F(3, 147) = 2.45, p = .066). The resultant functional data underwent spatial smoothing (6-mm FWHM Gaussian kernel) and removal of linear trends. After that, nuisance covariates including six head motion parameters, white matter signal, and cerebrospinal fluid signal were regressed out.

Blind HRF Deconvolution

The point process analysis (Tagliazucchi, Balenzuela, Fraiman, & Chialvo, 2012) was performed after noise signal regression to detect evoked and spontaneous point events in three task blocks and the resting condition, respectively. After that, the following steps were operated to deconvolute HRF: (1) BOLD fluctuations with large amplitude (>1 SD; detected by point process analysis) were collected and deemed as markers of significant neural events. The threshold of >1 SD rather than >3 SD was selected because the curve of SSBRs is sinusoid in which the peak value is about 1.4 SD (Wang et al., 2014; Wu, Liao, et al., 2013; Tagliazucchi et al., 2012; Vialatte et al., 2010). (2) The onsets of neural events were estimated for HRF reconstruction, (3) the HRF of each voxel was obtained by matching BOLD signal with canonical HRF and its time derivative, and (4) the Wiener deconvolution was used to recover neural level signals in each voxel (users. ugent.be/~dmarinaz/HRF deconvolution.html; Wu, Liao, et al., 2013; Wu, Stramaglia, Chen, Liao, & Marinazzo, 2013; Glover, 1999).

The SSBRs at the Whole-Brain Level

After HRF deconvolution, the power spectrum was obtained at the whole-brain level to examine whether the SSBRs were evoked by the semantic comprehension task. As operated in SSEP studies, the fast Fourier transform was used to convert the time course of the mean signal of the whole brain to the frequency domain. The resolution of full frequency range was 0.002 Hz (sampling rate/sampled data = 0.5 Hz/228). The power spectrum of each block was acquired in the gray matter using the automated anatomical labeling mask without cerebellum for each participant (Tzourio-Mazoyer et al., 2002). This gray matter mask was used because most of the energy metabolism appeared in the gray matter (Biswal et al., 1995). According to visual inspection, SSBRs were evoked at the fundamental frequency of stimuli and the first harmonic. The fundamental frequency indicates that the brain is driven by the flickering stimuli at precisely the stimulation frequency. The first harmonic shows that response frequency that is twofold of the stimuli frequency is evoked by the stimuli. Therefore, the repeated-measures ANOVA was conducted within the frequency intervals of 0.08-0.087 Hz (the fundamental frequency \pm 0.003 Hz) and 0.163–0.17 Hz (the first harmonic \pm 0.003 Hz). The mean power in each frequency band was fitted into ANOVA. Four blocks (three task blocks and one resting block) served as within-subject factors. Post hoc analysis was performed with SPSS Version 16 (SPSS, Inc., Chicago, IL) to test whether SSBRs were evoked in all three task blocks compared with the resting condition. Bonferroni's method was used to correct multiple-comparison error (Wang et al., 2013). To test the effect of HRF deconvolution, the SSBRs were also obtained before HRF deconvolution using the same method.

The Regional SSBRs

The amplitude of low-frequency fluctuations (ALFF, the square root of the power spectrum) obtained by the method of Zang et al. (2007) was utilized to examine the frequencyspecific power changes induced by the semantic comprehension task. The ALFF was calculated at each voxel in the aforementioned automated anatomical labeling mask within the frequency bands of the 0.08-0.087 and 0.163-0.17 Hz. The obtained ALFF values were transformed to standard z values to reduce the global effects of variability across participants (Yan & Zang, 2010). The regional SSBRs were computed before and after HRF deconvolution to determine whether the regional SSBRs were dependent on neurovascular coupling. The repeatedmeasures ANOVA was performed to examine regional differences of amplitude among the four blocks in each frequency interval. Post hoc analysis was performed with paired-samples t test. All resulting statistics were corrected using family-wise error (FWE) method (p < .05) for multiple comparisons (Worsley et al., 1996). Statistical analyses were conducted with SPM8 (www.fil.ion.ucl.ac. uk/spm).

Given the rigorousness of FWE correction, the statistical results may overlook some slight resonances. To obtain a finer inspection of SSBRs throughout the brain, we further computed the relative amplitude of task/resting for each block. The relative amplitude was based on the raw ALFF rather than the normalized ALFF because the latter included some zero values. The mean relative amplitude was then obtained as the average of relative amplitude of three blocks. Neural oscillations were deemed to be enhanced when the mean relative amplitude was larger than 1 and decreased when the mean relative amplitude was lower than 1.

The Relationship between SSBRs and RTs

Pearson correlation analysis was performed with SPM8 between SSBRs and RTs of three task blocks at the fundamental frequency and the first harmonic. Because the accuracy reached the ceiling, the correlation analysis was not performed between SSBRs and accuracy. To clarify whether the relationship between SSBRs and RTs was influenced by the baseline BOLD fluctuations, we further ran the correlation analysis between the ALFF of the resting state and mean RTs of three task blocks. The FWE method was used to correct multiple comparison errors.

RESULTS

Behavioral Results

The accuracy was $97.53\% \pm 4.38\%$, and the mean $\pm SD$ RT was 2760.67 ± 1073.56 msec for all sentences, indicating that 7 sec was sufficient for participants to react.

SSBRs of the Whole Brain

As shown in Figure 1, the semantic comprehension task evoked significant SSBRs at the fundamental frequency (0.08–0.087 Hz; before HRF deconvolution [BD]: *F*(3, 147) = 102.83, *p* < .001, partial η^2 = 0.701; after HRF deconvolution [AD]: *F*(3, 147) = 144.48, *p* < .001, partial η^2 = 0.747) and the first harmonic (0.163–0.17 Hz; BD: *F*(3, 147) = 18.44, *p* < .001, partial η^2 = 0.344; AD: *F*(3, 147) = 48.40, *p* < .001, partial η^2 = 0.497), indicating that SSBRs were induced at the whole-brain level and independent of the neurovascular coupling. Post hoc analysis revealed that the power of three task blocks was higher than that of the resting condition at the fundamental frequency (BD: *ts*(49) > 12.75, *ps* < .001, Cohen's *ds* > 1.72; AD: *ts*(49) > 13.74, *ps* < .001, Cohen's *ds* > 2.48; one-tailed) and the first harmonic



Figure 1. The power spectral of the whole brain before (A) and after (B) HRF deconvolution. Significant SSBRs are evoked at the fundamental frequency (0.083 Hz) and the first harmonic (0.167 Hz) by the semantic comprehension task.

(BD: ts(49) > 4.64, ps < .001, Cohen's ds > 0.94; AD: ts(49) > 6.92, ps < .001, Cohen's ds > 1.12), suggesting that the semantic comprehension task with a constant stimuli presentation frequency strikingly increased the variability of neural oscillations.

The Regional SSBRs

For the frequency band of 0.08–0.087 Hz, the highest SSBRs were observed in the bilateral VC, SMA, and the left fusiform gyrus (FG; Figure 2A), whereas the SSBRs were the highest in the bilateral VC and the left FG (Figure 2B) at the frequency interval of 0.163–0.17 Hz. Significant SSBRs were shown in the visual (VC), motor (SMA), and language (FG) areas, suggesting that the increased neural oscillations were task related. Of note, the HRF deconvolution did not exert significant influence on the spatial pattern of regional SSBRs (Figure 2). Furthermore, post hoc analysis showed that amplitudes in the abovementioned regions were higher in task blocks than in the resting condition, revealing remarkable resonance in these regions.

After further inspection of the spatial pattern throughout the brain (Figure 3), we found that SSBRs modulate widely brain regions rather than the aforementioned regions, in line with the previous finding that low-frequency oscillations modulate gross cortical excitability (Vanhatalo et al., 2004). Particularly, some language-related regions were regulated by the task, although SSBRs in language regions were weaker than those in sensory and motor regions. For example, the amplitudes in the left inferior frontal gyrus, left posterior temporal cortex, and bilateral insula in task blocks was as twofold as those in the resting condition. These results indicated that the sensory and motor regions are prone to be entrained by regularly presented stimuli than regions that are involved in higher-order cognition.

The Relationship between SSBRs and RTs

There were close relationships between SSBRs and RTs in the left OFC and SMA at the fundamental frequency (FWE correction, p < .05). These regions were shown in Figure 4 (center; peak Montreal Neurological Institute coordinate of OFC [BD: -33, 27, -18; AD: -33, 27, -18] and SMA [BD: -9, 12, 57; AD: -12, 12, 57] and cluster size of OFC [BD: 138, AD: 31] and SMA [BD: 62, AD: 35]). We further computed the mean RT and extracted the mean ALFF of three blocks for each participant. The correlation coefficients of mean RT and mean ALFF were .504 (BD) and .473 (AD) for the OFC and .316 (BD) and .357 (AD) for the SMA (Figure 4, peripheral panels). No region shows significant correlations between SSBRs and RTs at the first harmonic. Furthermore, there was no significant correlation between these two parameters in the resting condition, suggesting that the relationship between SSBRs and RTs is not because of the baseline fluctuations in these regions.

Figure 2. The regional SSBRs at 0.08-0.087 and 0.163-0.17 Hz. The highest SSBRs appear in the bilateral VC, SMA, and the left fusiform at the 0.08- to 0.087-Hz frequency band, whereas the highest SSBRs locate in the bilateral VC and left fusiform at the 0.163- to 0.17-Hz frequency interval. The HRF deconvolution does not strikingly change the spatial pattern of SSBRs. The regional SSBRs are visualized with the BrainNet Viewer (Xia, Wang, & He, 2013).



DISCUSSION

Neural oscillations are the essential characteristics of neural functions (Calderone et al., 2014; Schroeder & Lakatos, 2009; Ward, 2003). As a frequency-tagging method, the SSEP is powerful to uncover neural oscillation mechanisms of basic cognition. However, in the past, the SSRs in low frequency and in higher-order cognition have received little attention. After our prior study focusing on low-frequency steady-state neural oscillations (Wang et al., 2014), we explored the low-frequency SSRs in a semantic comprehension task. We revealed for the first time that higher-order cognition tasks could evoke SSBRs. In accordance with previous studies, the SSBRs were induced at the fundamental frequency and the first harmonic (Vialatte et al., 2010) and were independent of neurovascular coupling (Wang et al., 2014). However, the SSBRs in language processing regions were weaker than those in the visual and motor regions, suggesting that different brain regions have distinct sensitivities to repeated stimuli. Furthermore, the SSBRs in the left OFC and SMA were correlated to RTs, supporting the psychophysiological significance of SSBRs.

The Similarity between SSBRs and SSEPs

The harmonic phenomenon is a typical feature of SSRs (Vialatte et al., 2010) and is assumed to reflect the activities of the nonlinearly coupled neural systems (Roberts

Figure 3. The SSBRs

throughout the brain. The maps show the ratio of amplitude of task-resting. Besides the regions shown in Figure 2, responses in other language processing areas and task control regions are also enhanced to some extent. L = left; R = right.





Figure 4. The correlation between SSBRs and RTs was significant in the left OFC and left SMA at the fundamental frequency. Dots show the mean RT and ALFF of each participant. Solid lines show the linear correlation. Dashed lines show the 95% confidence interval.

& Robinson, 2012; Herrmann, 2001). In previous reports, the SSEPs were consistently observed at the fundamental frequency, several harmonics, and subharmonics of stimulus (Rossion, Prieto, Boremanse, Kuefner, & Van Belle, 2012; Rossion & Boremanse, 2011). Likewise, the SSBRs are evoked at the fundamental frequencies and the first harmonic, especially in the visual and motor regions. The observations of weaker strength and the limited number of harmonic regions are consistent with recent findings about SSEPs (Heinrichs-Graham & Wilson, 2012; Pastor, Valencia, Artieda, Alegre, & Masdeu, 2007); that is, the mechanisms might be different for fundamental and harmonic frequencies. Furthermore, SSBRs have been found to be stronger at 0.125 Hz than at 0.0625 Hz, and the SSBRs at 0.125 Hz are also task related (Wang et al., 2014). These results cannot be interpreted by low-power and high physiological noise; the findings indicate that SSBRs at the frequency range of >0.1 Hz also manifest task-related distributions and mechanisms. Therefore, different mechanisms for fundamental and harmonic frequencies are a reasonable interpretation for the discrepancy in the current study, although SSBRs may be more contaminated by physiological noise at the first harmonic than at the fundamental frequency. However, the mechanism of harmonic phenomenon is not fully understood. Our findings, therefore, provide a new way to understand the harmonic phenomenon in the low frequency range.

Because the SSBRs are reserved at the neural level, the similarities between the SSBRs and SSEPs may indicate that some rules in the high frequency range are appropriate for the low-frequency neural oscillations. In fact, some characteristics of complex systems have been shown in both high and low frequency ranges, such as the scale free (He, 2014) and small-worldness (Bassett & Bullmore, 2006). The cross-frequency relationship can also be established on the phase-amplitude coupling (Canolty & Knight, 2010). For instance, the coupling between the phase of infraslow frequency neural fluctuations and the amplitude of high-frequency neural oscillations has been reported (Thompson et al., 2014; Vanhatalo et al., 2004). As a vital characteristic of neural activities, the cross-frequency relationship has received more attention (Canolty & Knight, 2010). The relationship between SSEPs and SSBRs may provide novel insights into our understanding of the mechanism of cross-frequency relationships.

Of note, the role of HRF in SSBRs deserves more attention. The findings that SSBRs were largely insusceptible after HRF deconvolution and the proposal that BOLD variability is independent of HRF (Balsters, Robertson, & Calhoun, 2013; Baria et al., 2011) do not mean that SSBRs are totally uninfluenced by HRF. Given the evidence that the HRF greatly impacts BOLD signal in the infraslow (<0.1 Hz) frequency ranges (Robinson et al., 2006; Zarahn, Aguirre, & D'Esposito, 1997) and that the mechanism of HRF is not quite clear (Rosenegger & Gordon, 2015; Di, Kannurpatti, Rypma, & Biswal, 2013), the relationship between HRF and SSRBs warrants more studies.

Furthermore, the SSBRs have critical advantages over the SSEPs. First, high spatial resolution of fMRI allows better examinations of regional or deep brain variability. Second, the time scale of low-frequency BOLD fluctuations (often <1 Hz) is more appropriate for capturing the presentation frequency of complex stimuli than that of SSEPs. Third, the frequency range of BOLD signal is supplementary to the SSEPs and facilitates our understanding of low-frequency oscillations. Therefore, the SSBRs may supplement the application of SSRs in examining the higher-order cognition and low-frequency neural oscillations.

SSRs in Higher-order Cognition

To the best of our knowledge, this is the first study focusing on SSRs in higher-order cognition. Noticeable SSBRs were evoked in the visual, motor, and language regions. The SSBRs are the highest in the visual and motor systems, showing a sensorimotor bias. The sensorimotor bias has been observed in SSEPs (Tobimatsu, Zhang, & Kato, 1999; Galambos, Makeig, & Talmachoff, 1981) as well as in training studies (Guerra-Carrillo et al., 2014). For example, the plastic alterations in the sensory modalities take place after only a short training session (Powers, Hevey, & Wallace, 2012), whereas the plasticity of higherorder cognition occurs after a few days of learning (Mackey, Singley, & Bunge, 2013). These findings indicate that the sensory and motor regions have higher plasticity than the areas engaged in higher-order cognitions. Alternatively, the lower SSBRs in language processing regions may be because of the reason that power in these regions is close to the ceiling during the resting state. Therefore, it is hard to evoke SSBRs in these regions. However, this hypothesis may not be true because the power in these regions is lower than that in the visual region during the resting state (Baria et al., 2011; Zuo et al., 2010). Furthermore, BOLD variability has been demonstrated to be sensitive to neuroplasticity (Leo et al., 2012), indicating the association between SSBRs and neuroplasticity. Therefore, we provide additional evidence for the argument that the sensorimotor bias is not a result of the spatial limitation of SSEPs but the intrinsic characteristics of neuroplasticity (Guerra-Carrillo et al., 2014). As proposed by Thut and colleagues (2012), the entrained neural oscillations may promote neuroplasticity by the mechanism of long-term potentiation. Accordingly, we suggest that, like the observed neural variability, the SSBR is an important marker of neuroplasticity (Polanía, Nitsche, Korman, Batsikadze, & Paulus, 2012; Dorris, Pare, & Munoz, 2000); further verification is needed.

Furthermore, the SSBRs in the left OFC and SMA are positively correlated to RTs. The left OFC has been

shown to be related to naturally paced reading (Hofmann et al., 2014), whereas the SMA is involved in initiating an action and early evaluation of the outcome of that action (Bonini et al., 2014). The positive relationship between RTs and SSBRs in these regions indicates that larger SSBRs in these regions may be associated with longer RTs via weaker ability to read and monitor action. This result confirms that the more difficult a task is, the more brain resources are engaged (Garrett, McIntosh, & Grady, 2014), while indicating that BOLD variability is related to behavioral performance.

Potential Mechanisms of SSBRs

Contrary to high-frequency neural oscillations in SSEPs, the low-frequency neural oscillations in SSBRs represent a slow, cyclic regulation of gross cortical excitability (Vanhatalo et al., 2004) and serve as the activity baseline of the brain (Gusnard & Raichle, 2001). In this framework, the SSBRs are the reflection of the brain to periodic stimuli by increasing power in task-related regions. The task dependency of SSBRs is in line with previous findings of the modality specificity of SSEPs (Vialatte et al., 2010) and task dependency and region specificity of brain signal variability (Mišić, Mills, Taylor, & McIntosh, 2010). Although the signal variability has been demonstrated to be associated with behavioral performance, cognitive capacity, aging, and neural plasticity (Garrett et al., 2014; Grady & Garrett, 2014; Garrett, Samanez-Larkin, et al., 2013; Garrett, Kovacevic, McIntosh, & Grady, 2010; Ghosh, Rho, McIntosh, Kötter, & Jirsa, 2008), whether the regions with higher variability are located in areas defined by traditional activation method is debatable (Garrett et al., 2014; Wang et al., 2014; Garrett, Kovacevic, McIntosh, & Grady, 2013). The task-related SSBRs in this study may provide valuable evidence to support the hypothesis that regions with high signal variability and high mean signal may overlap to some extent.

The brain signal variability is not only task dependent but also constrained by the natural frequency (Rosanova et al., 2009). That is to say, the evoked SSR would be the largest at the natural frequency of a particular region. The natural frequency or "spectral fingerprints" (Siegel, Donner, & Engel, 2012; Siegel & Donner, 2010) has been confirmed in high frequency range by electrophysiological studies (Liu et al., 2014; Tobimatsu et al., 1999). Recent studies have shown the frequency-specific functional connectivity (Gohel & Biswal, 2015; Wu et al., 2008), amplitude (Zhang et al., 2015; Liu et al., 2013; Zuo et al., 2010), and regional homogeneity (Song, Zhang, & Liu, 2014), suggesting that frequency-dependent brain activities also exist in lowfrequency BOLD fluctuations. The multiple generative mechanisms of low-frequency neural oscillations also support regional-specific natural frequencies (Siegel et al., 2012; Rosanova et al., 2009; Sanchez-Vives & McCormick, 2000). More studies are required to unravel the spectral fingerprints in the low frequency range as well as the

relationship between regional spectral fingerprints and SSBRs.

Furthermore, the entrainment of neural oscillations has been emphasized in the understanding of cognitive processes (Calderone et al., 2014; Ward, 2003), such as sensory selection (Schroeder & Lakatos, 2009), attention focus (Calderone et al., 2014), and listening behavior (Henry & Obleser, 2012). Compared with previous studies of entrainment in the high frequency range, the roles of entrainment in the low frequency range are still unclear. The SSBRs, as the entrainment of low-frequency neural oscillations, are promising to fill this knowledge gap.

Limitations

Although we report important findings about SSBRs, a few limitations remain. For example, our participants only included young men. The SSR and brain variability are comparable in both genders but differ across age groups (Garrett, Samanez-Larkin, et al., 2013). Thus, we should confirm the findings in samples of other age groups. In addition, the resting state is always scanned before the task state. This avoids the interaction between both states but might induce the order effect. Although there are no trends of monotonic increasing or decreasing (Figure 1), it is unknown to what extent our findings are confounded by order effects. Future studies may counterbalance the order of multiple blocks to avoid the possible order effects. Another limitation is that physiological activities were not recorded during the task. Hence, it is impossible to regress out physiological noises directly and hard to evaluate the effect of denoising approaches. Although the BOLD variability has high signal-to-noise ratio (Vialatte et al., 2010) and is stable to noise interference (Li, Kadivar, Pluta, Dunlop, & Wang, 2012), future studies should record cardiac and respiratory signals and regress out their influences as much as possible to get pure task-related signal. Furthermore, a significant correlation between RT and SSBR was only observed in the OFC and SMA. The lack of physiological correlation of SSBR in other brain regions (e.g., the VC) may be related to the experimental design (e.g., the constant stimulus presentation time). Therefore, the physiological correlation of SSBR should be explored in future studies with various experimental paradigms. Finally, how SSBRs modulate neural oscillations at other frequency bands is out of the scope of this study but is an essential question for our understanding of the mechanisms of SSBRs and low-frequency neural oscillations.

Conclusions

In summary, we document a new index with the fMRI technique to explore how low-frequency neural oscillations are modulated by higher-order cognition. As the first study focusing on effects of higher-order cognition on SSRs, we revealed that SSBRs in low frequency range are similar to the SSEPs in the high frequency range. The SSBRs are evoked in task-related regions, independent of neurovascular coupling, and show sensorimotor bias. We further demonstrated the psychophysiological relevance of SSBRs, indicating that the SSBRs are a promising index in investigating the neural oscillation mechanisms of cognition. The exploratory work raised more questions than answers. The mechanisms of SSBRs warrant further study.

Acknowledgments

The work was supported by the 973 project (No. 2012CB517901), the 863 project (2015AA020505), the Natural Science Foundation of China (61125304), the Specialized Research Fund for the Doctoral Program of Higher Education of China (No. 20120185110028), and the Fundamental Research Funds for the Central Universities (ZYGX2013Z004).

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