

博士論文

Cross-frequency coupling as a mechanism to bind

varying types of information processing in the brain

(脳内の異なる情報処理を繋ぐメカニズムとしての周波数間カップリング)

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Purpose of research

Ever since Hans Berger identified brain rhythm (Berger, 1929), the rhythm has been studied intensively in neuroscience community. Successive researches illustrated the existence of different rhythms after Berger's discovery of alpha rhythm. However, a relationship between those rhythms remains unclear. In this dissertation, how brain rhythms interact with each other and play a role in information processing in the brain is discussed. Furthermore, the dissertation argues how brain rhythms drives spike, which is a fundamental unit of brain computation, to enable more efficient computation

Chapter 1 Introduction

1.1 Brain rhythm

Neural rhythm or oscillation is the essential part of information processing in the brain. Rhythms in the brain reflect the deflection of an electric field. All neuronal processes at a given point of the brain produce a potential, with relation to a reference. The negative spatial gradient of the potential is an electric field, which can be monitored by extracellular electrodes (Buzsáki et al., 2012). More precisely, the field is the superposition of ionic processes. The electric field is called as the electroencephalogram (EEG) when monitored from the scalp, as the electrocorticogram (ECoG) when monitored by subdural electrodes on the cortex, and as the local field potential (LFP) when monitored by electrodes inside 'in the brain' (Fig. 1).

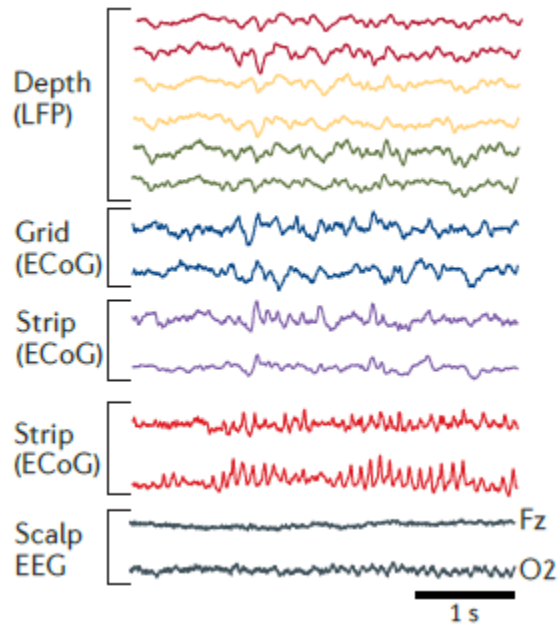


Figure 1. Signals from the same source recorded y different recording systems are different

(Buzsáki et al., 2012).

Transmembrane currents, which go through any sorts of excitable membrane, for instance, a spine, dendrite or axon, affects an extracellular electric field. From here onwards, the electric activity is called as LFP because neuroscientists often use the word to describe the field. In this dissertation, LFP will be analyzed in terms of oscillation. In comparison to event-related potential (ERP), which was an electrophysiological response to a stimulus or action and frequently used to search for neural correlates of human behavior (Luck 2014), there are some aspects of information processing in the brain, which can be quantified from the oscillatory perspective, for instance, regional interaction (Varela et al., 2001). The later chapters will discuss these things in detail. Two important characteristics of LFP oscillation are amplitude and phase (Figure. 2).

AMPLITUDE AND PHASE

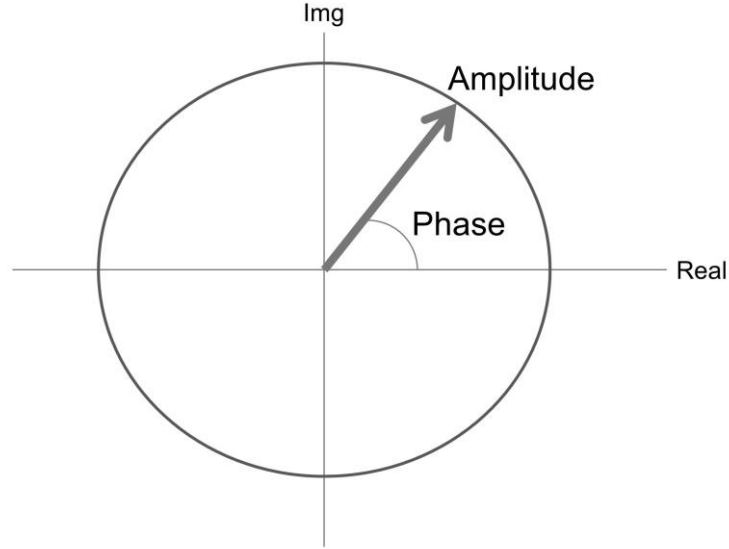


Figure 2. Amplitude and phase in complex-valued analytic signal. Amplitude is the length of the signal whilst phase is the angle of the signal.

Amplitude is determined as the difference of the magnitude over a period, whilst phase is defined as the deviation relative to the origin of wave cycle. When analyzing LFP, it is first decomposed into different frequency bands since different frequency bands have been associated with brain functions (Buzsáki, 2006). The most popular frequency decomposition technique is Fourier transform. It can transform time-series data to power spectrum, which is expressed as a function of frequency (Nunez 2006). Whilst temporal information is lost in Fourier transform, wavelet transform is able to derive frequency spectrum, whilst retaining temporal information. A mathematical function of wavelet is,

$$G(t, f) = \exp\left(-\frac{t^2}{2\sigma_t^2}\right)\exp(j2\pi ft)$$

where f , t and j stand for frequency, time and imaginary unit, respectively (Lachaux et al., 1999). This equation produces instantaneous complex-valued signals, from which the derivation of amplitude and phase are possible.

The brain has functionally meaningful multiple frequency bands. In the rat's brain, there are at least 10 distinctive frequency bands (Fig. 3), each of which has different associated functions (Pennttonen and Buzsáki , 2003) .

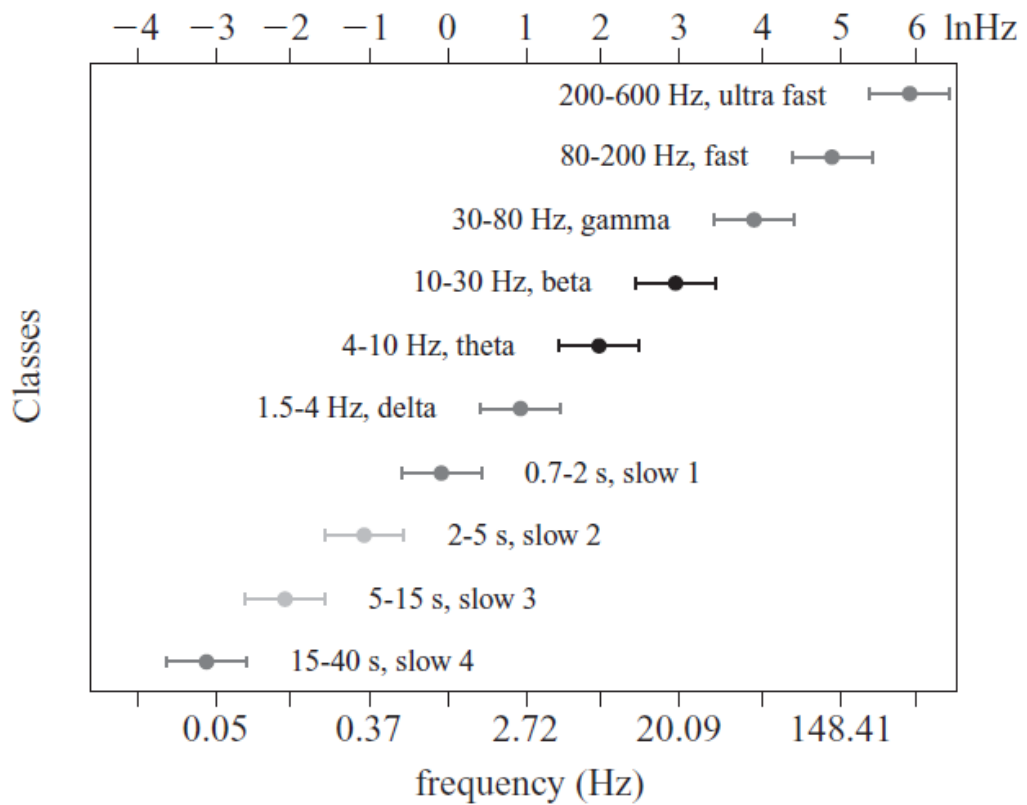


Figure 3. Distinctive oscillatory classes of the rat brain. The mean frequencies of bands progress based on log-scale (Penttonen and Buzsáki , 2003). Oscillatory classes in the human brain are slightly different from the rat. The 4 - 30Hz are usually divided into theta (4-8 Hz), alpha (8-14 Hz) and beta (14 – 30 Hz) (Deuschl et al., 1999).

Magnitude of LFP power is roughly the inverse of temporal frequency. Generally, higher frequency oscillations have smaller amplitude whilst lower frequency oscillations have larger amplitude (Buzsáki and Mizuseki, 2014). A part of the differences is that in higher frequency oscillations, a less number of neurons could fire in one cycle whereas in lower frequency more neurons could be activated (Buzsáki et al., 2012). It should be noted that all of the frequency activities are present during any type of tasks, however, relative strength of frequency components differs depending on behavior. Therefore, LFP is informative with respect to understand how the brain works differently with behavior. Exemplary relationships between brain functions and human LFP bands are; delta band in memory consolidation during slow-wave sleep (Lee et al., 2002), theta band in working memory (Jensen and Tesche, 2002) and alpha and beta bands with the motor system (Pfurtscheller and Lopes da Silva, 1999).

LFP oscillation has two-forms of activity in relation to stimulus; evoked and induced. (Tallon-Baudry and Bertrand, 1999). Evoked oscillations are phase-locked to a stimulus. It could be measured by averaging responses. Furthermore, these responses can be biased by attention (Henry et al., 2004; Tiitinen et al., 1993). On the other hand, induced oscillations are not cue-locked. Averaging those signals vanish the response. Analytical methods have to change based on whether the signals are evoked or induced.

The relativity in strength of LFP frequency components is due to the differential contribution of the distinctive sources in the brain. Extracellular signals picked up from an electrode consist of synaptic activity, action potential and after-hyperpolarization-potential (AHP) (Buzsáki et al., 1988). However, the contribution of synaptic activities is the largest (Nunez and Srinivasan, 2006), and it could be divided into two main components; cellular-synaptic structural organization and their temporal synchrony of the dipole moments (Buzsáki et al., 2012). Because of the difference across brain regions in these two components, the strength of LFP also differs. In the cortex, LFP are particularly strong. Pyramidal cells, which are the most dominant type in the cortex, have the apical dendrite running in

parallel with each other. Therefore, the neurons create synchronous and substantial dipoles and generate an open field, where the sink is considerably far from the return currents. This leads to ionic flow and large LFP. On the other hand, spherically symmetric neurons, for instance, thalamocortical cells, have dendrites of roughly same size projecting in every direction, and create nonsynchronous and small dipole. This leads to generate a closed field, where the sink is considerably close to the return currents. Therefore, the contribution to LFP is relatively small (Lorente., 1947; Lindén et al., 2010). Since pyramidal neurons do not exist in the thalamus and cerebellum, LFP recorded from the regions is relatively small (Buzsáki et al., 2012).

Action potential or spike, is a rapid fall and rise of membrane potential of a single neuron and regarded as fundamental for information processing in the brain (Kandel et al., 2000). The relationship between spike and LFP, are complex. Spike is microscopic signal in comparison to LFP. LFP, which is macroscopic signal, has differential contributions from all sorts of neuronal processes (Buzsáki et al., 2012). Generally LFP per se has no correlation with spike (Rasch et al., 2008), since somatic inhibition, which contributes to LFP, sometimes suppresses the generation of spike. However, looking at the signal in frequency domain, high-frequency component of LFP has eventually correlation with spike. Particularly, LFP power higher than 100Hz has strong correlation with spike frequency and synchrony (Ray and Maunsell ., 2010; Zanos et al., 2011). Furthermore, high frequency activity of LFP is associated with a specific layer in which cell bodies and axon terminals are concentrated (Quilichini et al., 2007). Therefore, LFP, which is macroscopic signal, could give insight into the microscopic process of action potential (Crone et al., 2011; Belluscio et al., 2012; Rasch et al., 2008; Miller et al., 2007).

A neuroscience experiment on human subject frequently uses EEG to measure LFP. One of the strengths EEG has its excellent temporal resolution compared to fMRI. However, whilst an fMRI is able to illustrate detailed spatial information, EEG has several confounding factors that render difficult to derive meaningful insights into spatial information (Nunez and Srinivasan, 2006). For instance, a distance

between an electrode and the source affects the signals recorded. As the currents travel through brain tissues, other currents coming from different sources also add up. Because of this, it is hard to interpret where the signals come from (Buzsáki et al., 2012). Current source density transformation (CSD) is one way to solve this problem. It is a measure to enable relative localization of activities (Mitzdorf, 1985). The difference, which CSD reflects, is the volume density of the net current going in and out the extracellular areas. Suppose that three electrodes put in equal distances between each other monitor a distant current source (Figure 4).

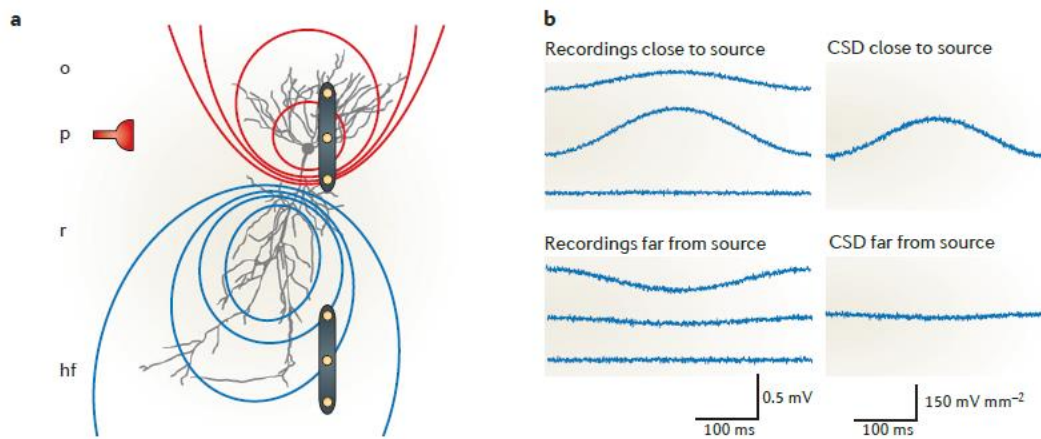


Figure 4. Two cases for three electrodes recording brain signals. If the electrodes are located closely to the current source, the difference of the signals recorded from each electrode is relatively large. On the other hand, the difference of the signals recorded by electrodes, which are far apart from the source, is relatively small. This indicates that the localization of the current source is to some extent possible exploiting whether the voltage difference is large or small (Buzsáki et al., 2012).

Each recording site has different distance to current source. Therefore, there is voltage difference between the electrodes. If the current sources were far away from the recording sites, the difference in measured voltage between the electrodes would be smaller. On the other hand, if the electrodes were close to the

current source, the difference would be much bigger. In other words, the current source is close. Using CSD and looking at the voltage difference, relative estimation of the current source, meaning whether it is close or distant, is possible (Buzsáki et al., 2012). Furthermore, localizing the current sources further is possible since the physics of how the extracellular potential originates is largely understood (Nunez and Srinivasan, 2006; Buzsáki et al., 2012). Indeed, Ohm's law and known information about the conductance of brain tissues allows estimating the current flow between two recording sites. These procedures and high-density recording techniques can determine the location of the current source or sink. Therefore, it is possible to infer the microscopic sources from the macroscopic signals. Taken together, LFP, which is the electric field measured in the brain, can inform about important aspects of brain activities.

1.2 Information processing in the brain

In this chapter, how synchrony and cross frequency coupling (CFC) in LFP signals that are associated with information processing in the brain will be reviewed.

Synchrony

The concept of synchrony came from physics. It is defined as the modulation of oscillations due to their weak interactions (Pikovsky et al., 2003). In neuroscience, synchrony is the co-modulations of the membrane potential in neural populations. Neurons fluctuate together not only at local scale (< 1 cm) but also at large scale (> 2 cm) (Varela et al., 2001).

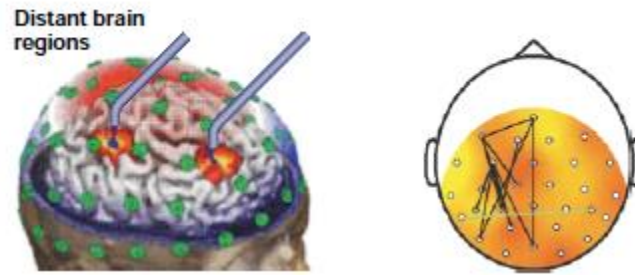


Figure 5. Schematic illustration of large-scale synchrony between regions. (Varela et al., 2001)

Looking at the brain from the perspective of synchrony, or network, gives insights into how the brain works. For instance, a vast repertoire of our behaviors cannot be fully accounted by the structure of the brain alone. The flexibility relies on functional interaction of the regions. This could be intuitively understood, taking an example of object recognition. Sensory systems, which are necessary to recognize objects, are distributed across specialized cortical areas. Moreover, computations in those regions run in parallel. Therefore, processed information in the regions must be integrated (Eckhorn et al., 1988 ; Gray and Singer., 1989 ; Singer and Gray, 1995). Visual objects, for instance, consist of color, edge, shape, etc. The brain has specialized regions for processing these features and the integration of the computations allow us to see the objects (Eckhorn et al., 1988; Engel et al., 1991 ; Kreiter and Singer, 1996 ; Fries, 2005). Furthermore, integration does not confine to intra-modality and can extend to inter-modality, since cognition and action take place usually in multi-sensory circumstances (Bollimunta et al., 2011). A notable example is a sensory motor integration. Playing a piano needs to bind auditory and motor information (Roelfsema et al., 1997). The auditory and motor cortex, which processed the information, are far apart. Without a mechanism to integrate the computation in the regions with fine temporal resolution, namely synchrony, human being would never be able to play works of, say, Liszt.

Furthermore, synchrony acts as a gating mechanism of action potential. Action potential generated in a neuron has higher probability in triggering the receiving neuron to fire when the receiving

neuron's membrane potential is most excitable. On the other hand, when the receiving neuron is least excitable, the neuron is less likely to generate spike (Engel et al., 1997; Womelsdorf et al., 2007). This interaction mechanism by synchrony is modifiable and can vary as a function of expectancy, prior knowledge and experiences (Engel et al., 2001; Fries et al., 2001; Uhlhaas et al., 2006). Furthermore, attentional processes can bias the interactions. Attentional bias on synchrony has been reported in stimulus selection, multimodal integration, working memory, and conscious processing of stimuli (Singer, 1999; Schnitzler and Gross, 2005 ; Varela et al., 2001).

There are two proven methods to quantify synchrony. First of all, coherence is a measure reflecting co-variance of the amplitude from different sites (Andrew and Pfurtscheller, 1996). On the other hand phase synchrony is an index independent of amplitude (Lachaux et al., 1999; Tass et al., 1998) (Fig. 5).

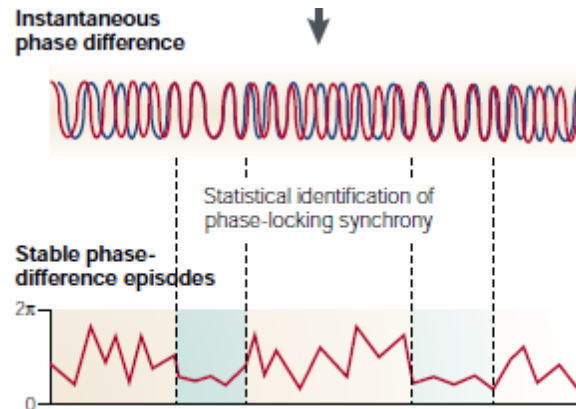


Figure 6. Schematic illustration of phase synchrony. After applying wavelet or Hilbert transform, phase difference of two different signals are compared to observe whether there is stable phase difference. If the difference is stable across time or trials, synchrony is present (Varela et al., 2001)

However, both reflect synchronization between neural populations anyway (Rodriguez et al., 1999; Bressler et al., 1993). Synchronization mainly is supported by cortico-cortical interactions

including inter-hemispheric interaction. Severing the corpus callosum abolishes the interhemispheric synchronization altogether (Engel et al., 1991). Anatomically cortico-cortical synchronization arises from excitatory connections (Schmidt et al., 1997). The magnitude of synchronization between recording sites and their distance have correlation; the closer the distance is, the higher the synchronization is (Kopell et al., 2000; Schnitzler and Gross, 2005; von Stein and Sarnthein, 2000). Moreover, measurement limitation of a recording system confounds the relationship between the regional distance and synchrony. For instance, a pair of nearby electrodes tends to have higher synchrony because the electrodes pick up more signals from common current sources. Transforming the value for synchronization into the magnitude of the deviation from the baseline could deal with the confounding factor (Rodoriguez et al., 1999).

Synchronization in different frequency bands has distinctive roles. Higher frequency synchronization tends to occur within a close distance whereas lower frequency synchronization tends to occur in a longer distance (Palmer et al., 2000). For instance, two ECoG electrodes have higher correlation in theta band when the electrodes are far apart, whilst gamma oscillation has higher correlation when the distance is close (Sederberg et al., 2003). Over all, lower frequency activities modulate the interaction between distant regions, whereas higher frequency activities modulate activities over the small distance. However, higher frequency synchrony is desirable when interaction of information processing should be in precise timing, even if the distance is long, since the interaction can be more finely tuned (Fries et al., 2001).

Although synchronization is ubiquitous across brain regions, some doubts about whether it truly carries information or not (Shadlen and Movshon, 1999). The problem arises because synchronization cannot be completely distinguished from rate coding in general. Rate coding is a hypothesis that the frequency of spikes carries information. In the motor system, for instance, rate coding reflects population vector of movements, which is the preferred directions of neurons (Georgopoulos et al., 1986). Furthermore, synchronization in the motor cortex does not provide additional information with

respect to the direction of movements, in relation to the frequency discharge of neurons (Oram et al., 2001). What makes the matter more complicated is that as the number of spikes goes up, accidental temporal contingency of spikes between neurons become higher (Uhlhaas and Singer, 2006). Consequently, spurious synchronization could arise. Some studies were eventually against synchronization as a binding mechanism, and argued that co-variation of spike rate is the alternative mechanism (Nirenberg et al., 2001; Roelfsema et al., 2004). However, Riehle et al. (1997) showed that when monkey formed stimulus expectancy, synchronization alone, but not firing rate, varied. Interestingly, when the subjects were actually responding to external stimuli, modulation of both spike frequency and synchronization occurred together. Furthermore, Grammont and Riehle (2003) demonstrated the dissociation of firing rate and spike synchronization in the execution of movements using monkey. Depending on the period of the task, they found higher synchronization with lower firing rate and lower synchronization with higher firing rate. To summarize, spike rate coding and synchronization could be a complimentary mechanism.

Cross-frequency coupling (CFC)

So far, neural oscillations with different frequency have been discussed independently. However, those barely act on their own but interact with each other. This means that the brain integrates information processing with different temporal scale. Recently, hierarchical relation of oscillations has been proposed that slower frequency oscillation controls higher frequency oscillations (Lakatos et al., 2005; Palva et al., 2005) through phase-amplitude coupling, which is reviewed here.

Phase-amplitude coupling

The most documented cross-frequency coupling is phase-amplitude coupling. It describes the dependence of higher frequency amplitude on lower frequency phase.

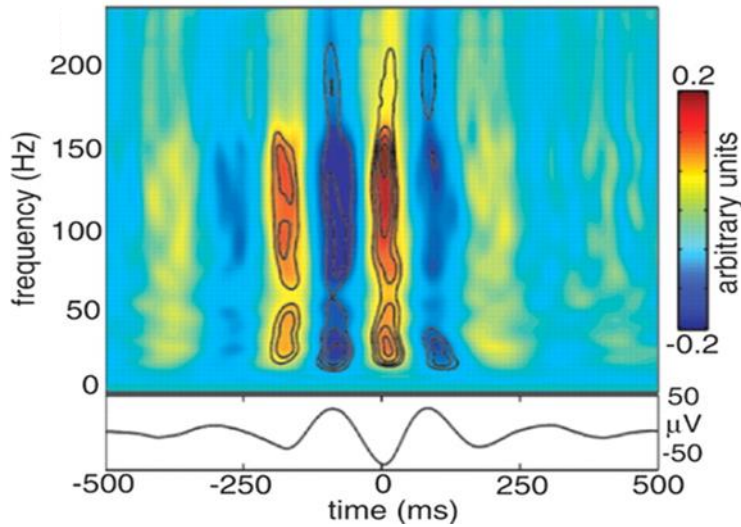


Figure 7. Example of phase amplitude coupling. The magnitude of gamma amplitude (heat map) depends on lower frequency phase (waveform) (Canolty et al., 2006).

Slower neural oscillations reflect cortical excitability, and the degree of excitability changes depending on the phase (Canolty et al., 2006). Higher cortical excitability is associated with the trough of a slower oscillation, whereas lower cortical excitability is linked to the peak of the oscillation (Fries, 2005). Therefore, in the trough of slower oscillations, stimulus-driven spikes are more likely to occur (Giraud and Poeppel, 2012). In other words, phase amplitude coupling could be the mechanism to concentrate the generation of spike, such that efficient computation is possible (van Atteveldt et al., 2014). This principle could be generalized to long-range interaction (Womelsdorf et al., 2007; van Elsvijk et al., 2010). For instance, spikes generated in a given region could arrive at a differential phase of slower oscillation in the target area. When the oscillation in the area is in the trough, arriving spikes would be processed more efficiently than when in the peak. Namely, arriving spikes likely to affect regional computation more, when the phase and amplitude are coupled. Additionally, phase-amplitude coupling is even more

important, considering a report that lower frequency phase is entrained by external stimuli (Schroeder et al., 2008; Canolty and Knight, 2010). External stimuli in the world are often periodic but the rhythms are mostly slower than fast spike computation of the brain. Therefore, the way to adjust brain's fast computation to slow external stimuli is needed, and phase-amplitude coupling would make it possible by combining slow oscillations with faster rhythms. Hence, phase-amplitude coupling is also a plausible mechanism to integrate external information by slow oscillation with much faster spike computation of the brain.

Phase-amplitude coupling is quantified by the statistical dependence of higher frequency amplitude on lower frequency phase. It has been extensively studied in human (Uhlhaas and Singer, 2006). Brain regions in which the coupling has been observed include the hippocampus (Buzsáki et al., 2003; Hentschke et al., 2007; Wulff et al., 2009), basal ganglia (Tort et al., 2008), and cortex (Lakatos et al., 2005; Canolty et al., 2006). Theta-gamma coupling is most frequently reported among types of the coupling. A seminal work by Canolty et al. (2006) showed that the coupling is almost ubiquitous across many cortical regions. Interestingly, the spatial configuration of the coupling varies depending on behavior.

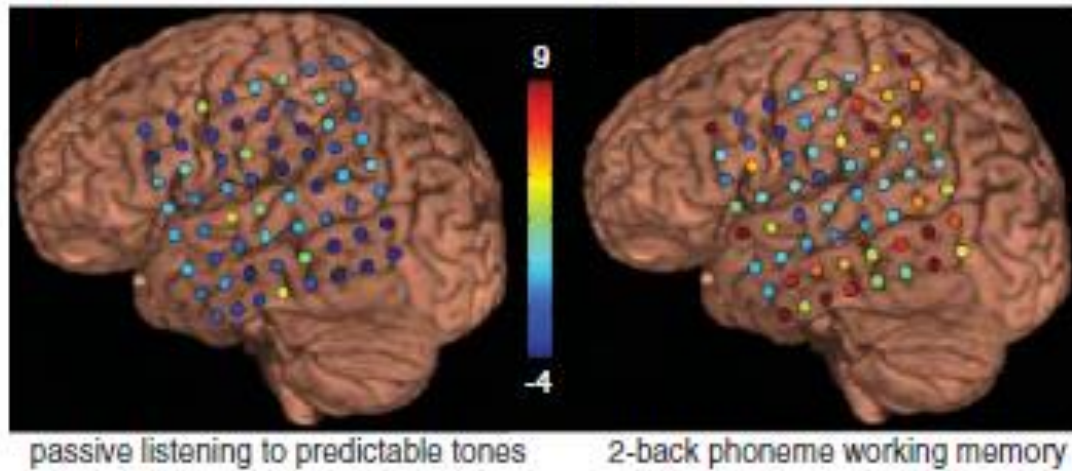


Figure 8. Hot spots of theta-gamma phase amplitude coupling changes as the tasks change. Both of passive listening to predictable tones and 2-back phoneme working memory tasks had the significant coupling (Canolty et al., 2006). The positivity and negativity of the coupling indicated phase-amplitude coupling and decoupling, respectively. The strength of the coupling in each electrode differed over the tasks.

However, gamma oscillation is not only modulated by theta phase but also by other rhythms. For instance, Voytek et al. (2010) reported that occipital gamma was controlled by alpha phase during a visual task, whilst during an auditory task theta phase modulated gamma amplitude. Whitting stall et al. (2009), on the other hand, reported delta-gamma phase amplitude coupling in the visual cortex of monkey. Given structural differences in cortical areas and their spike statistics, it is no wonder if multiple phase-amplitude couplings exist in our brain. Cross-frequency coupling has at least other two types ; phase-phase coupling, and amplitude-amplitude coupling.

Phase-Phase coupling

Phase-phase coupling is also a reasonable mechanism to integrate computations with different temporal scales. However, it remains unclear whether it is functionally relevant to neural computation directly.

Studies, which suggest the involvement in neural computation, showed that spike rate during learning was correlated with spike rate in the same region when in non-REM sleep. This could be interpreted as the replay of learning during sleep as phase-phase coupling since spike rate in the sleep is 6 times faster than the original one (Euston et al., 2007; Johnson et al., 2010). Therefore, this is 1:6 phase-phase coupling. In a similar manner, temporal compression of spike computation is observed in the hippocampus, suggesting a possible role of phase-phase cross-frequency coupling in the brain computation (Nadasdy et al., 1999).

Physiology and challenge of cross-frequency coupling

Cross-frequency coupling could arise from statistical dependence alone, namely spurious relationship. Research on cross-frequency coupling could be only meaningful when it has an underlying mechanistic coupling of spikes and synaptic activities. Indeed, that theta and gamma are coupled is physiologically equivalent to that there is a coupling between the pyramidal neuron and interneuron sub-networks (Bao et al., 2003; Whittington et al., 2003; Hutcheon et al., 2000; Canolty and Knight, 2010). When optogenetic methods have inhibited GABAergic inhibitory interneuron network, the effects selectively appeared in gamma and theta-gamma coupling (Wulff et al., 2009; Bartos et al., 2007; Cardin et al., 2009). Furthermore, Buzsáki et al. (2012) suggested the general mechanism of cross frequency coupling. Cell assemblies are networks of neural population. For given computation, the different assemblies are activated sequentially or in parallel. Phase activity integrates those distinctive assemblies, and then the integrated assemblies is processed by amplitude computation.

1.3 Motor system and neural synchrony

Amplitude modulation in motor control

Ever since Hans Berger has discovered alpha (8-12 Hz) oscillations which varied as subjects opened and closed eyes (Berger, 1929), neural synchrony has been regarded as the essential way for information processing in the brain. Later, Adrian and Matthews (1934) demonstrated that the rhythm originated from the occipital regions. Additionally they revealed another rhythm with the same frequency range but coming from an area near the central sulcus. Together with that rhythm, beta oscillation which showed the reduction of amplitude in the same region was also found (Jasper and Andrews, 1938). Those two rhythms were later called Rolandic rhythm (Pfurtscheller, 2003). Rolandic rhythm modulates with voluntary, involuntary and imaginary movements as well as the preparation (Jasper and Penfield, 1949; Chatrian et al., 1964; Pfurtscheller and Andrew, 1999). Ever since the discovery, the classification of other oscillations based on the association with brain function and behaviour has been attempted.

Oscillations in the brain are self-sustaining. When there are no inputs, neural populations produce rhythmic activities. This in fact led to the idea that alpha and beta oscillations are ‘idling’ rhythm (Adrian and Matthews, 1934; Pfurtscheller et al., 1996; van Wijk et al, 2012). Recently, alpha rhythm is rather believed to actively regulate cortical inhibition, whereas the role of beta rhythm is unclear yet although it could signify at least partially the similar function (Klimesch et al., 2007; Engle and Fries 2010). In line with the concepts, alpha and beta oscillations in the primary motor cortex show decreases in amplitude prior to and during movements, suggesting the release of inhibition. This reduction rebounds following the movements and exceeding the resting state level (Pfurtscheller and Lopes Da Silva, 1999). The reduction in amplitude is coined as event-related desynchronizations (ERD) and the increase event-related synchronization (ERS). These phenomena have varying magnitude depending on several parameters. For instance, force in movements produces larger ERD in alpha and beta bands (Stancak and Pfurtscheller, 1996; Stancak et al., 1997; Mima et al., 1999) and longer ERS (Stancak et al., 1997).

Furthermore, the more muscle fibers are involved, the longer ERS lasts, as this has been demonstrated in comparison of finger, wrist, and shoulder movements (Pfurtscheller et al., 1998; Stancak et al., 2000). Moreover, higher frequency of movements lead to stronger beta ERD and weaker ERS, and the increase of the frequency further render ERD and ERS less noticeable (Toma et al., 2002; Houweling et al., 2010). Finally, alpha and beta ERD increases as the complexity of movements rises (Pfurtscheller, 2003).

Alpha and beta rhythms are to some extent independent and have different roles to play in some cases. Beta rhythm is suggested to preserve status quo (Engel and Fries, 2010). For instance, beta rhythm but not alpha rhythm shows the increase of amplitude in tonic muscle contraction. This is perhaps because tonic muscle contraction needs stabilization of force. Additionally, spatial distribution of alpha and beta rhythms are different. Alpha ERD prior to a movement is initially more spatially spread, and if the movement is retained the phenomena become spatially focused. On the other hand, beta ERD appears in a localized fashion in the first place (Crone et al., 1998.) However, both the ERDs become lateralized when either of both hands is specified to respond (Gilbertson et al., 2005; van Wijk et al., 2009). The contralateral motor cortex shows larger reduction in amplitude in comparison to the ipsilateral cortex. Furthermore, beta ERS than alpha ERS is more recognizable although it ends faster (Salmelin and Hari, 1994; Pfurtscheller et al., 1996; Erbil and Ungan, 2007). Such phenomenal differences could be at least partially due to having the different origins. Alpha rhythm originates from the somatosensory cortex, whilst beta rhythm originates from the motor cortex (Salmelin and Hari, 1994; Cheyne et al., 2008; Ritter et al., 2009). What are the physiological mechanisms of ERD and ERS? Transcranial magnetic stimulation study indicates the decrease of corticospinal excitability during alpha and beta ERS, suggesting the suppression of cortical excitability by both rhythms (Jancke et al., 2006). Indeed, pyramidal tract neurons increase their spiking activities when power and synchrony of beta LFP in the given population decreases (Baker et al., 2001; Spinks et al., 2008). Pfurtscheller et al. (1996) argued that alpha and beta ERS reflects the recovery from the activated state to the resting state.

Some argue that gamma and alpha/beta appear against with each other. ECoG, EEG, and MEG studies have showed the increase of gamma activity before and around movement onsets when alpha/beta ERD was pronounced (Pfurtscheller and Neuper, 1992; Pfurtscheller et al., 1993; Ohara et al., 2001; Pfurtscheller et al., 2003; Cheyne et al., 2008; Muthukumaraswamy, 2010). LFP in macaque monkey showed the consistent results. Gamma synchrony was prominent in the primary motor cortex before the initiation of movements (Sanes and Donoghue, 1993). Interestingly, synchrony was particularly high when subjects engaged in exploratory movements in comparison with the resting state (Murthy and Fetz, 1996). Gamma increase was recognizable in the contralateral motor cortex, but not in the ipsilateral side. (Szurhajetal., 2005; Miller et al., 2007). Furthermore, gamma has subdivision. Low (35 – 50 Hz) and high (75 – 100 Hz) frequencies play different roles. Low-gamma amplitude increases after the initiation of movements whilst the increase of high-gamma amplitude begins earlier but lasts for a short time (Ball et al., 2008). To summarize, gamma band activity contributes to the execution of movements, whilst beta rhythm is mainly involved in sustaining initiated movements. This is in line with the views that beta is to maintain status quo and that gamma correlates with spike activities (Buzsáki et al., 2012). Additionally, alpha rhythm regulates cortical inhibition (Klimesch et al., 2007).

What have been discussed so far are about oscillations in a relatively localized area of the brain. However, as discussed in the previous section, neural oscillations have an active role in ‘binding’ information. For the visual system, it is understood that neural synchrony integrates parallel computation of, say, edge, color, surface etc. to produce the perception of an object (Eckhorn et al., 1988; Engel et al., 1991; Kreiter and Singer, 1996;). However, the relevance of neural synchrony in the motor systems remains unclear. Some argue that components of motor program are distributed in different neural population, and cell assemblies arise via synchrony when the motor program is in demand (Wickens et al., 1994; Hommel, 2004). Indeed, movements require distant multiple regions including the cortical and subcortical areas as well as the spinal cord, in order to execute. The necessity of a way to link

computations in the distant areas is obvious.

Corticospinal synchrony

When the cortex and spinal cord communicate with each other, synchrony would be a candidate for the underlying mechanism. Corticospinal synchronization can be bi-directional. Cortical areas could entrain motor neuron projecting to the spinal cord, and the peripheral neural activities could entrain the activities in the motor cortex (Lemon and Van der burg, 1979). However the efferent connection is stronger than the opposite (Mima et al., 2001; Brovelli et al., 2004).

A motor neuron produces a motor unit action potential to contract muscle. In order to increase the force level, the spike rate of motor neurons becomes higher with the frequency range from 6 Hz in the resting state to 120Hz in the case of ballistic movements.(Freund, 1983; van Wijk et al., 2012). Synchronization between the primary motor cortex and contralateral muscle has its most prominent frequency as beta band, especially during tonic contraction of muscle (Conway et al., 1995; Salenius et al., 1997; Witte et al., 2007; Chakarov et al., 2009). Interestingly, when subjects produced the maximal force, the synchronization frequency shifted to gamma band (Mima et al., 1999). In addition, gamma corticospinal synchronization increases when the adjustment of the force is necessary (Schoffelen et al., 2005; Andrykiewicz et al., 2007; Omlor et al., 2007). Notably, alpha synchronization has not often been reported in the corticospinal synchrony and varied across participants if found (Salenius et al., 1997; Mima et al., 1999). When a cognitive task was introduced, corticospinal synchrony rather decreased (Mat Safri et al., 2007; Johnson et al., 2010).

Cortico-cortical synchrony

A number of studies have suggested possible roles of cortico-cortical synchrony in brain functions. Beta synchrony between the motor and visual cortex became higher in a visuo-motor task. The

increase disappeared when the visual stimulus was only a distractor, therefore not relevant to the movements per se (Classen et al., 1998). When subjects were doing auditory-motor task, alpha band synchrony increased between the primary motor cortex, auditory cortex, supplementary motor area, premotor cortex, cerebellum and thalamus (Pollok et al., 2005). Furthermore, the supplementary motor area, which contributed to the execution of voluntary movements, has exhibited synchrony with varying magnitude according to task demands. Synchrony between the supplementary motor, sensory motor and premotor areas was increased in self-initiating movements in comparison with externally-paced movements (Classen et al., 1998; Serrien 2008). Moreover, beta band synchrony appeared in the interhemispheric relationship between the motor regions in, interestingly, unimanual and bimanual movements (Mima et al., 2000; Gross et al., 2005). This was confirmed in monkey studies as well (de Oliveira et al., 2001). When a task was more difficult, this interhemispheric synchrony increased. (Manganotti et al., 1998; Gross et al., 2005). However, as subjects were accustomed to a novel or difficult task, interhemispheric synchrony rather decreased (Andres et al., 1999; Serrien and Brown, 2003). To summarize, inter-regional synchrony plays a role in the motor system, and flexibly adjusts the magnitude depending on task demands and learning.

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Causality of rhythms and behavior

It has long been a subject of a debate whether brain rhythms are causally involved in the generation of behavior or just epiphenomena. Recent development of transcranial alternate current stimulation (tACS) enables to directly test the causality between brain rhythms and behaviors by inducing oscillation externally. Pogosyan et al. (2009) illustrated that entrainment of beta rhythm (20 Hz) made the initiation of movements slower whilst 5 Hz stimulation did not produce the same effect. Convincingly, the execution of movements became slower when beta rhythms spontaneously bursted in the resting state (Gilbertson et al., 2005). Furthermore, Chen et al. (2006) showed that 20Hz deep brain stimulation

induced awkwardness in movements, whilst much higher frequency ameliorated the symptom of Parkinson's disease (Kuhn et al., 2006; Weinberger et al., 2006; Ray et al., 2008). Furthermore, directional flow of information can be estimated using causality analysis such as granger causality and transfer entropy (Nolte et al., 2008; Muskulus et al., 2009; Mima et al., 2001).

Chapter 2

Abstract

Oscillatory activity plays a critical role in the brain. Here, we illustrate the dynamics of neural oscillations in the motor system of the brain. We used a non-directional cue to instruct participants to prepare a motor response with either the left or the right hand and recorded electroencephalography during the preparation of the response. Consistent with previous findings, the amplitude of alpha-band (8–14 Hz) oscillations significantly decreased in the motor region contralateral to the hand prepared for response. Prior to this decrease, there were a number of inter-regional phase synchronies at lower frequencies (2–4 Hz; delta band). Cross-frequency coupling was quantified to further explore the direct link between alpha amplitude and delta synchrony. The cross-frequency coupling of showed response-specific modulation, whereby the motor region contralateral to the preparation hand exhibited an increase in coupling relative to the baseline. The amplitude of alpha oscillations had an unpreferred and a preferred delta phase, in which the amplitude was modulated negatively and positively, respectively. The amplitude of alpha-band oscillations decreased over the analyzed period, indicating that negative modulation of alpha-band oscillations in the unpreferred delta phase was stronger than positive modulation in the preferred phase. Therefore, the amplitude of alpha-band oscillations was down-regulated by the phase-amplitude coupling. Taken together, these results show global-to-local computation in the motor system, which started from inter-regional delta-phase synchrony and ended at an effector-specific decrease in the amplitude of alpha-band oscillations, with phase-amplitude coupling connecting both computations.

Introduction

Oscillations in the brain mediate a number of functions. Electroencephalography (EEG) frequency-specific activity in vivo is classically classified as delta (1–4 Hz), theta (4–8 Hz), alpha (8–14 Hz), beta (12–30 Hz), and gamma (30–75 Hz) (Canolty and Knight, 2010). Each band was associated with particular functions; for instance, delta band has been associated with memory consolidation in slow-wave sleep (Lee et al., 2002), theta band with working memory (Jensen and Tesche, 2002), alpha and beta bands with motor preparation and execution (Pfurtscheller and Lopes da Silva 1999) and gamma band with attention (Womelsdorf and Fries, 2007). However, cross-frequency interactions between the bands recently attract increasing attention (Canolty and Knight, 2010).

In the motor system, alpha-band activity (mu rhythm) is inhibitory. Low-amplitude alpha oscillations reflect active neural processing whereas high-amplitude alpha oscillations are a signature of inhibition (Klimesch et al., 2007). A reduction in the amplitude of alpha oscillations is termed event-related desynchronization (ERD) and an increase is called event-related synchronization (ERS) (Pfurtscheller and Lopes da Silva, 1999). ERD and ERS occur before and after movements, respectively (Pfurtscheller, 2003), and can occur in the part of the motor regions which represents the part of the body involved in the movement. (Pfurtscheller, 2003). However, executing movements requires the interaction of multiple non-motor regions of the brain (Ledberg et al., 2007). Global interactions between brain regions form transient neuronal networks that enable large-scale integration of information (Gray et al., 1989; Singer, 1999; Tallon-Baudry and Bertrand, 1999; Varela et al., 2001; Kitajo et al., 2007). Recently, phase synchrony of brain activity has been proposed as a measure of this large-scale integration (Varela et al., 2001). Information conveyed through a large-scale interaction might give rise to local interactions (Kawasaki et al., 2010; Fell and Axmacher, 2011). As alpha ERD occurs just before the execution of a movement, we reasoned that there should be global interactions between multiple regions prior to the ERD. Moreover, we reasoned that such inter-region communications would manifest as phase synchrony

at frequencies below the alpha band, given that lower and higher rhythms are associated with global and local interactions, respectively (Buzsáki and Draguhn, 2004; Jensen and Colgin, 2007).

To investigate the relation between alpha and lower-frequency oscillations, we focused on cross-frequency coupling. Lakatos et al. (2005) proposed the oscillatory hierarchy hypothesis, whereby the amplitude of relatively higher frequency oscillations is controlled by the phase of lower frequency oscillations. Furthermore, Canolty and Knight (2010) argued that cross-frequency coupling could be the mechanism by which global information processing is relayed to local information processing. But it is yet to be illustrated by further experimental evidence. Taking these studies into account, our hypothesis was that inhibition and disinhibition through alpha-amplitude is regulated by information transmitted in the phase of synchronous oscillations at lower frequencies. Additionally, we hypothesized that such a relation between alpha and lower frequencies would be measured by phase-amplitude coupling measurement in a function-specific way.

Materials and Methods

Participants

Twenty healthy participants (14 males & 6 females, 20–39 years old, right-handed) were tested in this study. Before the experiment, all participants provided informed consent. The study was approved by the RIKEN ethics committee. All participants had normal or corrected-to-normal vision and no neurological or psychiatric disorders.

Experimental paradigm and stimulus presentation

Participants were instructed to perform a cued response task, which was a variant of the Posner paradigm (Posner, 1980). A 17-inch CRT monitor (CPD-E220, SONY, Japan; 100 Hz refresh rate) was placed 100 cm away from the participant. Participants were seated and maintained their head position with a chin rest. Figure 9 depicts a schematic illustration of the experimental time course. Participants were asked to fixate

on a central dot throughout the experiment. A trial started with a horizontal line superimposed on the central dot. After 500 ms, a colored square (cue stimulus) appeared in the same place as the central dot. The cue stimulus was presented for 100 ms. The size of the central fixation dot, the horizontal bar, and the cue and target stimuli was 0.1 visual degrees, 0.1 vertical visual degrees, and 1 horizontal visual degree and 1 visual degree, respectively. The cue and target stimuli were purple, green, or yellow. The three colors were randomly associated with the three responses (right/left/no) across subjects.

Participants held a video game controller (Razer hydra, Sixense Entertainment, USA) in each hand. The controller contained a button that could be pressed by the thumb and they were instructed to prepare a response with the right or left thumb or no response based on the color of the cue stimulus. Left-hand preparation, right-hand preparation, and no preparation conditions will be referred as ‘Left’, ‘Right’, and ‘No’, respectively. After the cue stimulus, white noise in terms of space was displayed for 10 ms to eliminate the visual adjustments to the color. A second colored square (target stimulus) was then displayed after a delay of 1020–1720 ms (uniform distribution to produce random jitter). The target stimulus was displayed in the same place as the cue stimulus, and was presented for 150 ms, followed by white noise for 10 ms. The color of the target stimulus was identical to that of the cue stimulus for 75% of the trials. Regardless of the color of the cue stimulus, participants were instructed to respond according to the color of the target stimulus. The response required was indicated by the color of the stimuli rather than the position or shape of the stimuli to exclude the influence of visuospatial information. In the present paper, we present the results from the preparation period (1–1000 ms after the onset of the cue stimulus).

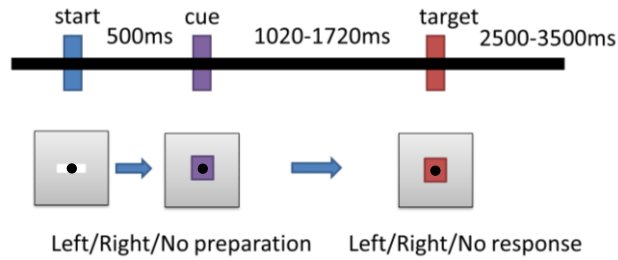


Figure 9. Schematic illustration of the experiment. Stimuli were squares in three colors. Each color was associated with a particular response: Button press with the left thumb (Left), button press with the right thumb (Right), or no response required (No). Subjects were required to prepare a response based on the cue stimulus and subsequently execute the response based on the target stimulus. In this paper, only data from the preparation period (1-1000 ms after the onset of the cue stimulus) are presented.

Procedure

Participants performed a training session of 32 trials to accustom themselves to the time course of a trial and the arbitrary association between the color of the stimuli and the required response. Participants then completed four blocks of 160 trials per block. After each block, participants were allowed to have a rest for as long as they wished.

EEG recording

EEG data were amplified and recorded using a BrainAmp MR+ system (Brain Products, Germany) and an EEG cap with 63 scalp electrodes (Ag/AgCl) configured in accordance with the international 10-10 system (EasyCap; EASYCAP GmbH, Germany), which was for higher-density electrode configuration. The EEG data were sampled at 1000 Hz and filtered from 0.015 Hz to 250 Hz. The midfrontoanterior (AFz) electrode was used to ground the signal. Electrode impedance was maintained below 10 kohm. EEG signals were referenced to the averaged recordings from the electrodes on the right and left earlobes. Electrodes placed above and below the left eye recorded activities related to vertical eye movements and

eye blinks and electrodes placed at the temples recorded activities related to horizontal eye movements. In the offline analysis, trials with EEG signal that exceeded $\pm 150 \mu\text{V}$ in any electrode were discarded.

EEG data preprocessing

Trials with artifact-free EEG data were segmented into 1.5-s epochs from 500 ms before to 1000 ms after the onset of the cue stimulus. We applied current source density (CSD) transformation to the EEG voltage distribution on the surface of the scalp by the spherical Laplace operator, to reduce the influence of volume conduction (Perrin et al., 1989). The algorithm estimates the current from the underlying neural population at a given electrode, which radially goes through the skull and scalp (Kayser and Tenke, 2006). The parameters of the operator were as follows: order of the spline = 4, maximum degree of the Legendre polynomial = 50, with a precision of 10^{-6} (Perrin et al., 1989).

EEG processing

Wavelet analysis

Instantaneous amplitude and phase were computed by convolving the CSD transformed EEG signal $s(t)$ with a complex Morlet wavelet function defined as:

$$w(t, f) = \sqrt{f} \exp\left(-\frac{t^2}{2\sigma_t^2}\right) \exp(i2\pi ft),$$

where σ_t denotes the standard deviation of the Gaussian window. The wavelet is shaped by how many cycles n_{co} reside in a $6\sigma_t$ interval (Lachaux et al., 1999). In the current study, $n_{co} = 3$ ($=6f\sigma_t$) was chosen, with the central frequency f spanning 1 to 45 Hz in 1-Hz steps. Wavelet transform was applied to a 5-s epoch of data from 2500 ms before to 2500 ms after the onset of the cue stimulus to eliminate the edge artifact with in the 1.5-s epochs.

Phase locking value (PLV)

The PLV (Lachaux et al., 1999) was used to quantify phase synchrony between CSD transformed EEG signals from two electrodes. The PLV describes the consistency of the phase difference between two

signals across trials. For electrodes i and k at time t , PLV is calculated as:

$$PLV_{ik}(t) = |\sum_{n=1}^N \exp(j(\varphi_i(t, n) - \varphi_k(t, n)))|,$$

where N is the number of trials and $\varphi(t, n)$ is the instantaneous phase in trial n at time t . The derived quantity (range, 0–1) represents the degree of phase locking. The greater the PLV, the stronger the phase consistency between the two electrodes. However, PLV tends to be larger between proximal electrodes, therefore, to normalize the distance of electrodes (Rodriguez et al., 1999), PLVz was calculated as follows:

$$PLVz = \frac{PLV_t - \text{mean}(\text{baselinePLV})}{\text{std}(\text{baselinePLV})}$$

Baseline PLV was calculated from –500 to –300 ms relative to the onset of the cue stimulus.

Modulation index

The method introduced by Canolty et al. (2006) was used to quantify phase-amplitude coupling. The method was applied only to data from electrodes C3 and C4, which were located over the motor region of the left and right (or right and left) hemisphere, respectively. The modulation index reflects the strength of coupling between the phase and amplitude of different frequencies. It is based on the complex variable;

$$z(t) = A_1(t) \exp(j\varphi_2(t)) \quad ,$$

where $z(t)$, $A_1(t)$, and $\varphi_2(t)$ represent the composite complex value, the amplitude at a given frequency, and the phase at another frequency, respectively. The raw modulation index (M_{raw}) is the absolute mean vector of the complex variable as follows:

$$M_{\text{raw}} = \left| \frac{1}{T} \sum_{t=1}^T z(t) \right|$$

In the current study, M_{raw} was calculated on a trial-by-trial basis by averaging the values over the time window from 1 to 1000 ms after the onset of the cue stimulus. Assuming that phase-amplitude coupling is a product of a specific pairing of phase and amplitude, we shuffled phase and amplitude values within a

trial to create surrogate data. This surrogate data approach enabled us to correct for different amplitudes across trials. M_{raw} was normalized as follows, to give the normalized modulation index (M_{norm}):

$$M_{norm} = \frac{M_{raw} - \mu_{surrogate}}{\sigma_{surrogate}}.$$

Finally, M_{norm} was averaged across trials for each subject.

Normalized mean amplitude of a specific phase

To explore the detailed relation between amplitude and phase across different frequencies, instantaneous amplitude normalized by the temporal mean and standard deviation of a given frequency was assigned to one of 12 binned phases of another frequency. Then, the mean amplitude on each of the 12 phase bins was calculated. These original data were compared to the surrogate data.

Statistical analysis

Data were averaged across trials before statistical analysis. The average amplitude and PLV across trials were compared across conditions (Left, Right, No) using a permutation test (Burgess and Gruzelier, 1999; Melloni et al., 2007). The paired permutation test flips the values of two conditions within each participant. After permuting the data 5000 times for the amplitude, 5000 times for the normalized modulation index, and 80000 times for PLV, the probability of the original data based on the distribution of permuted data was obtained. The precision of probability values obtained from permutation test relies on the numbers of permutation. The numbers were chosen to reach the sufficient precision to correct the probability values with respect to multiple comparison problems. False discovery rate (FDR) correction was applied to each point of the time-frequency chart for all electrodes (amplitude data) and all possible pairs of electrodes (PLV) (Benjamini and Hochberg, 1995). The number of hypotheses was 63 and 1953 for amplitude data and PLV data, respectively.

For comparing normalized modulation index in C3 and C4, a cluster-based permutation test

(5000 times) for two-dimensional data (frequency for phase and frequency for amplitude) was carried out (Maris and Oostenveld, 2007) and Bonferoni-corrected for the number of electrodes.

To test the significance of the mean amplitude of a specific phase, the confidence interval was calculated based on a surrogate data approach (1000 times) that randomly coupled original amplitude and phase data.

Results

Behavior

The average performance over all conditions in 20 subjects was a accuracy rate of 94.4 with a SD of 10.1% with an RT of 426.1 with a SD of 95.1 ms (RT was computed on correct trials only). A repeated-measures ANOVA was performed. There was a significant effect of preparation hand (Left/Right/No) on accuracy ($F(2,18) = 5.6281, p = 0.0072$), with the most accurate for Left preparation conditions, the second most accurate for Right preparation conditions, and the least accurate for No preparation conditions. There was a significant effect of preparation hand on RT ($F(2,18) = 66.5, p < 0.0001$) with the slowest for No preparation conditions, the second slowest for Left and the fastest for Right conditions. There was no significant effect of response hand (Left/Right) both on accuracy rate ($F(2,18) = 0.0231, p = 0.8808$) and on RT ($F(2,18) = 0.004, p = 0.949$). Furthermore, there was a significant interaction between preparation hand and response hand on RT ($F(1,19) = 31.35, p < 0.0001$), with No-Left, No-Right, Left-Right, Right-Left, Left-Left, Right-Right conditions in the order from the slowest to the fastest. Finally the significant interaction between preparation hand and response hand was observed on accuracy ($F(1,19) = 7.9936, p = 0.0013$), with Left-Left, Right-Right, Left-Right, Right-Left, No-Right, No-Left conditions in the order from the most accurate to the least accurate.

Amplitude difference related to motor preparation

Left and Right conditions were compared to the No condition. C3/C4 electrodes were selected to

represent the motor regions and O1/O2 electrodes were selected to represent the occipital regions (Figure 11).

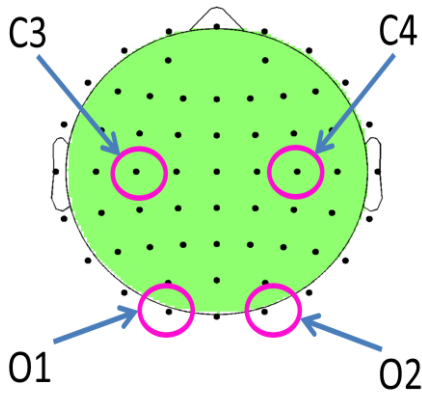


Figure 10. Schematic illustration of the electrodes chosen to represent the motor (C3/C4) and occipital (O1/O2) regions.

The No condition involves the same visual stimuli as the Left and Right conditions; therefore, low-level processing of visual stimuli in Left and Right conditions should be entirely eliminated by this comparison. In the Left condition, there was a significant decrease in the amplitude of oscillations at a frequency of around 12 Hz that first appeared in the occipital cortex about 350 ms after the onset of the cue stimulus (Figure 12C and D).

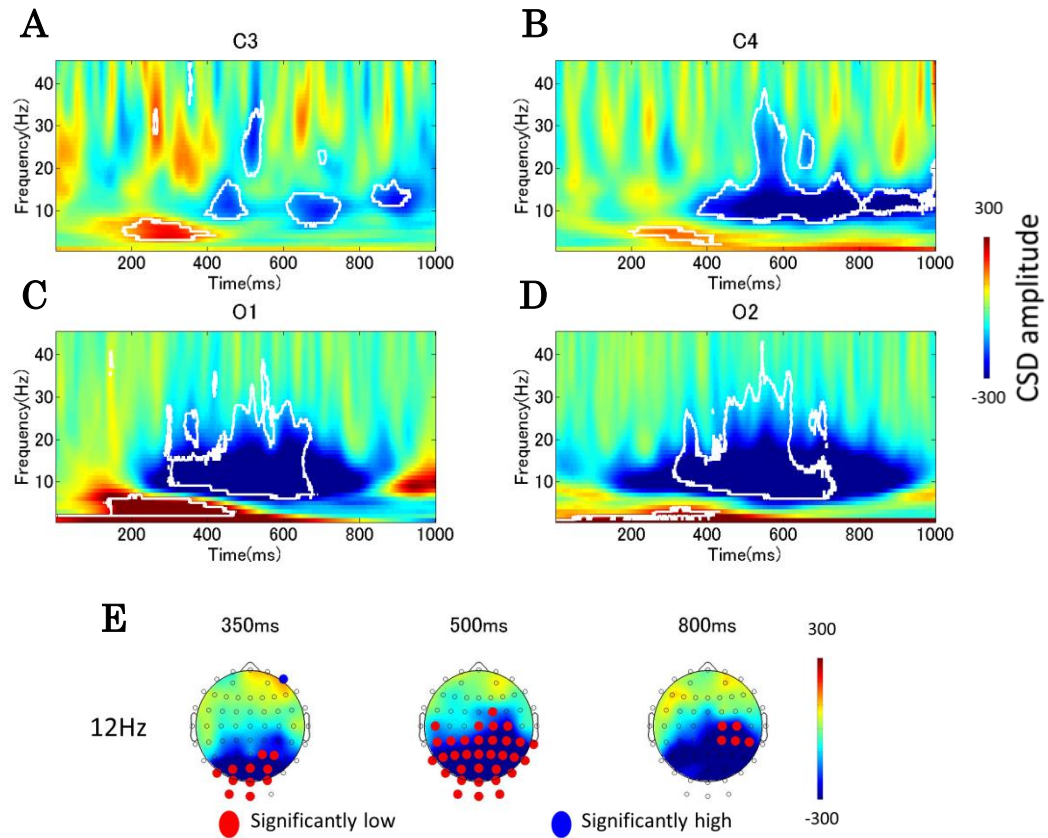


Figure 11. The amplitude of the current source density (CSD) at frequencies from 1 to 45 Hz and the time course of global modulation of amplitude at 12 Hz in the Left condition relative to the No condition after the onset of the cue stimulus. A–B: amplitude at C3 (A) and C4 (B); the two electrodes selected to represent the motor regions. C–D: amplitude at O1 (C) and O2 (D); the two electrodes selected to represent the occipital regions. The amplitude showed is amplitude in the Left condition minus amplitude in the No condition, averaged across all 20 participants. The amplitude showed alpha lateralization. Areas inside white lines indicate significance ($P < 0.05$, permutation test, FDR-corrected). E: amplitude at 12 Hz at 350, 500, and 800 ms after the onset of the cue stimulus at all electrodes. Red and blue circles indicate significant differences ($P < 0.05$, permutation test, FDR-corrected). Areas inside white lines indicate significance.

At the end of the preparation period, only the motor region contralateral to the side of motor preparation exhibited a significant decrease of 12 Hz amplitude (permutation test $P < 0.05$, FDR corrected; Figure 11A and 11B). In the Right condition, a significant decrease of peak-alpha 12 Hz amplitude first appeared in the occipital cortex at 400 ms after the onset of the cue stimulus (Figure 13C and D). At the end of the preparation period, only the motor region contralateral to the side of motor preparation exhibited a significant decrease of 12 Hz amplitude (permutation test $P < 0.05$, FDR-corrected; Figure 11A and B)

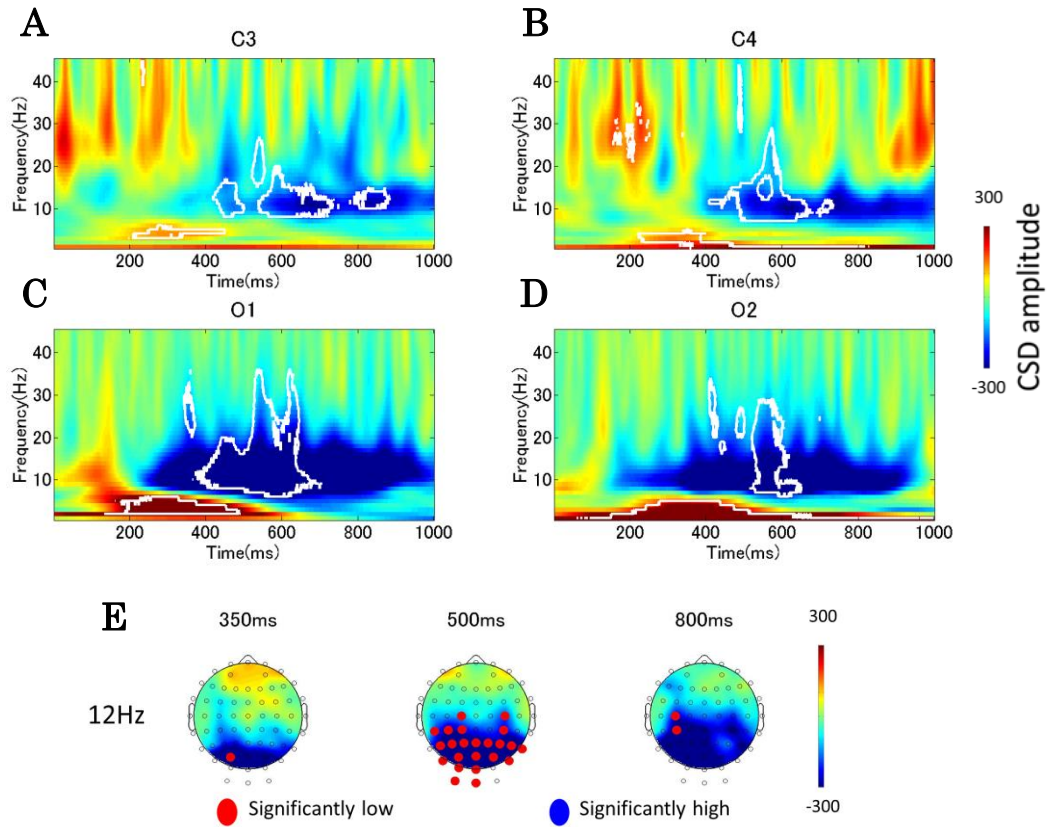


Figure 12. The amplitude of the current source density (CSD) at frequencies from 1 to 45 Hz and the time course of global modulation of amplitude at 12 Hz in the Right condition relative to the No condition after the onset of the cue stimulus. A–B: amplitude at C3 (A) and C4 (B); the two electrodes selected to represent the motor regions. C–D: amplitude at O1 (C) and O2 (D); the two electrodes selected to represent the occipital regions. The amplitude showed is amplitude in the Right condition minus amplitude in the No condition, averaged across all 20 participants. The amplitude showed alpha lateralization. Areas inside white lines indicate significance ($P < 0.05$, permutation test, FDR-corrected). E: amplitude at 12Hz at 350, 500, and 800 ms after the onset of the cue stimulus at all electrodes. Red and blue circles indicate significant differences ($P < 0.05$, permutation test, FDR-corrected).

Amplitude difference between the Left and Right conditions

To investigate the effector-specific modulation of brain activity, we assessed whether the cue stimulus

induced alpha lateralization, which has previously been observed in a somatosensory attention task according to the hand to which the participants attended (Haegens et al., 2011). The averaged amplitude was compared across the Left and Right conditions by subtracting the Left condition from the Right condition (Figure 14). Significant decreases in the amplitude of alpha-band oscillations were observed only in the left hemisphere (Figure 14A and C), and significant increases were observed only in the right hemisphere (permutation test $P < 0.05$, FDR-corrected) (Figure 14B and D). In the motor regions, significant alpha lateralization occurred between 600 and 800 ms after onset of the cue stimulus. In the occipital regions, significant alpha lateralization occurred around 800 ms.

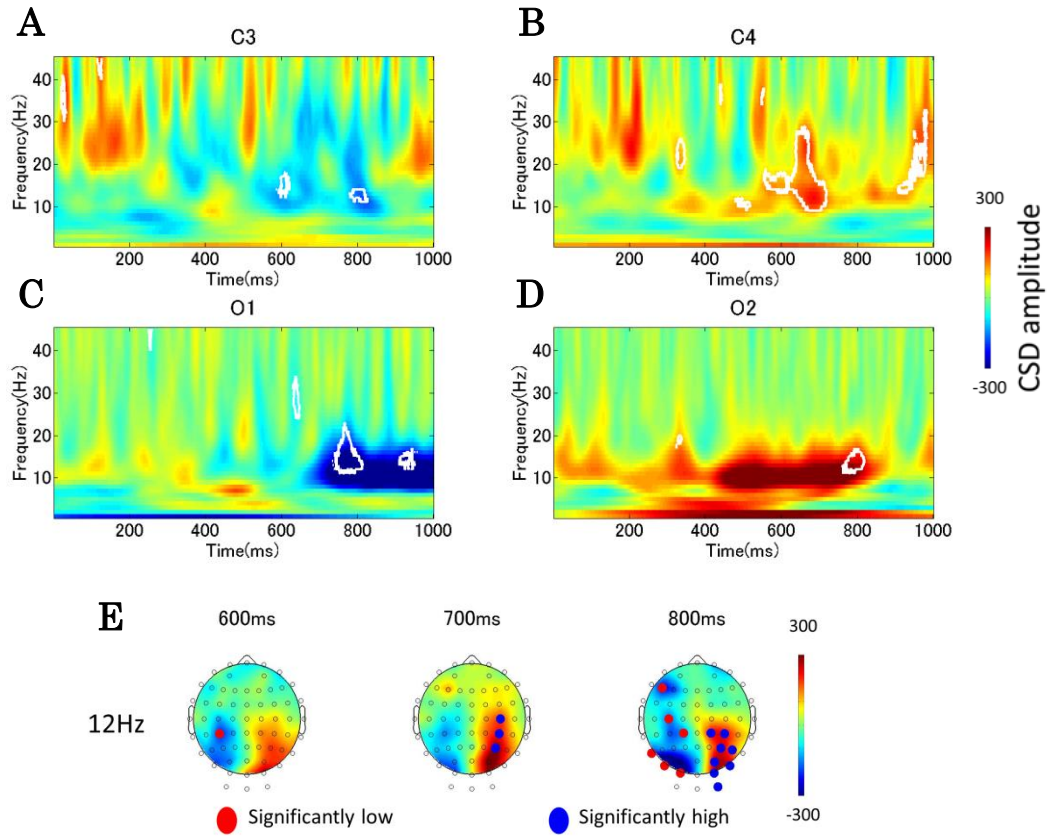


Figure 13. The amplitude of the current source density (CSD) at frequencies from 1 to 45 Hz and the time course of global modulation of amplitude at 12 Hz in the Right condition relative to the Left condition after the onset of the cue stimulus. A–B: amplitude at C3 (A) and C4 (B); the two electrodes selected to represent the motor regions. C–D: amplitude at O1 (C) and C4 (D); the two electrodes selected to represent the occipital regions. The amplitude showed is amplitude in the Right condition minus amplitude in the Left condition, averaged across all 20 participants. The amplitude showed alpha lateralization. Areas inside white lines indicate significance ($P < 0.05$, permutation test, FDR-corrected). E: amplitude at 12 Hz at 600, 700, and 800 ms after the onset of the cue stimulus at all electrodes. Red and blue circles indicate significant differences ($P < 0.05$, permutation test, FDR-corrected). Areas inside white lines indicate significance.

Delta phase synchrony

To investigate the possibility that effector-specific modulation of alpha amplitudes was caused by prior formation of transient neural assemblies, we computed the 1–45 Hz PLV for all possible electrode pairs (1953 pairs from 63 electrodes). The results were FDR corrected for the number of pairs and the Left and Right conditions were compared to No condition. For both the Left and Right conditions, PLV was significantly increased only at frequencies below 4 Hz (Figure 6). No electrode pairs showed a significant decrease of PLV when Left and Right conditions were compared with No condition. A significant increase of PLV at low frequencies (2–3 Hz) was observed around 300 ms after the onset of the cue stimulus in several of the electrode pairs that around 300ms (permutation test $P < .05$, FDR-corrected).

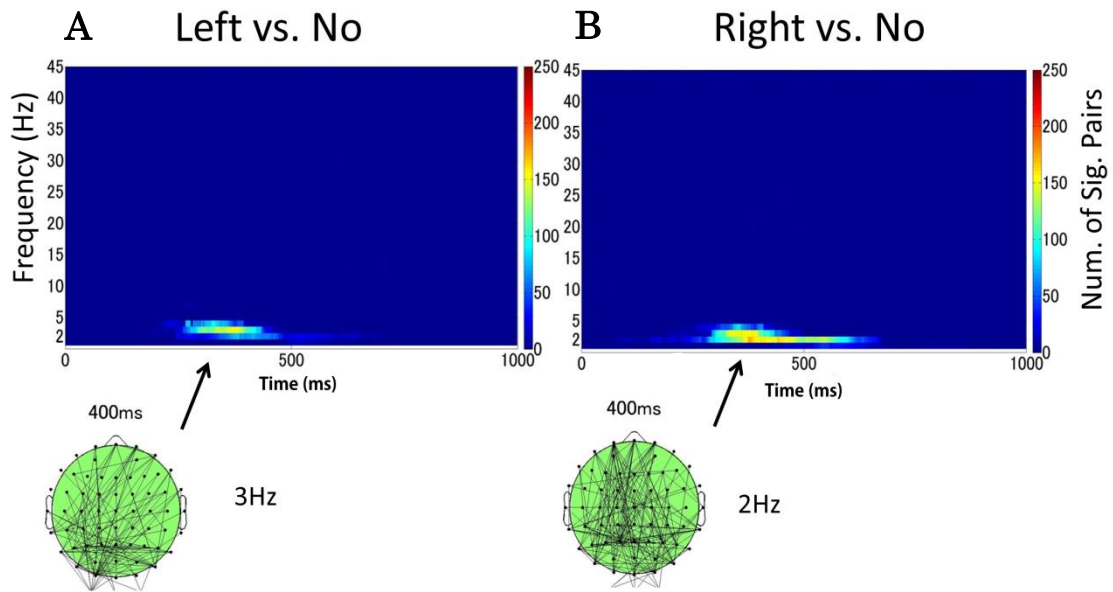


Figure 14. Time frequency maps after the onset of the cue stimulus. The number of electrode pairs with significantly different phase synchrony from all possible electrode pairs in the Left and No conditions (A) and the Right and No conditions (B) at frequencies from 1 to 45 Hz. Significance was determined as FDR-corrected $P < 0.05$, according to the permutation test. The comparison of the Left and Right condition did not yield any significant differences and therefore is not showed.

Cross-frequency coupling in the motor regions

To further investigate the relationship between delta phase synchrony and alpha amplitude modulation in motor preparation, we performed cross-frequency coupling analysis between delta phase and alpha amplitude. For all pairs of 1-4 Hz phase and 8-14 Hz amplitude, subject-averaged normalized modulation indices were significant for Left and Right conditions ($P < 0.05$, Bonferroni corrected; Figure 7).

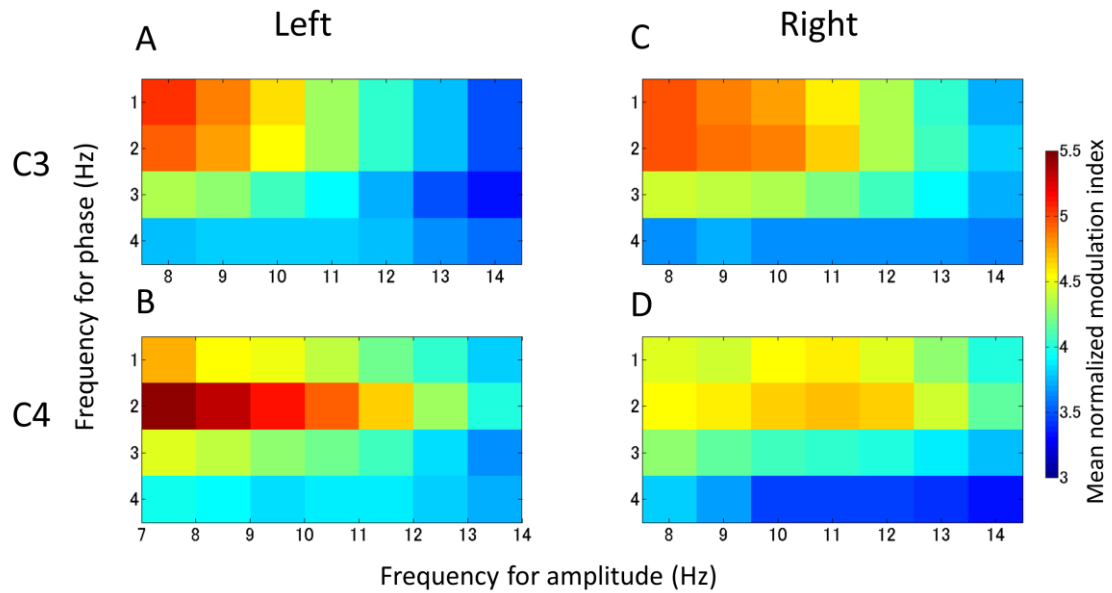


Figure 15. The normalized modulation index for the left (c3) and right (c4) motor regions for different combinations of phase (range, 1–4 Hz) and amplitude (range, 8–14 Hz). A: The normalized modulation index for the C3 electrode (the left motor region) during preparation in Left trials. B: The normalized modulation index for the C3 electrode during preparation in Right trials. C: The normalized modulation index for the C4 electrode (the right motor region) during preparation in Left trials. D: The normalized modulation index for the C4 electrode during preparation in Right trials. Data are averaged across all 20 subjects.

A cluster-based permutation test for M_{norm} was applied to Left/No and Right/No comparisons for data recorded from C3 and C4 (Figure 15). Significant clusters were only identified in the motor region contralateral to the side of motor preparation, i.e., C3 for the Right/No comparison and C4 for the Left/No comparison. One significant cluster in C3 for the Right/No comparison was identified, for pairs with 2- or 3-Hz phase and 11–14-Hz amplitude ($P < 0.001$, Bonferroni-corrected) (Figure 8A). Two significant clusters in C4 for the Left/No comparison were identified: one for pairs with 4-Hz phase and 11–14-Hz amplitude and one for pairs with 2-Hz phase and 8–10-Hz amplitude ($P < 0.001$, Bonferroni-corrected) (Figure 9B).

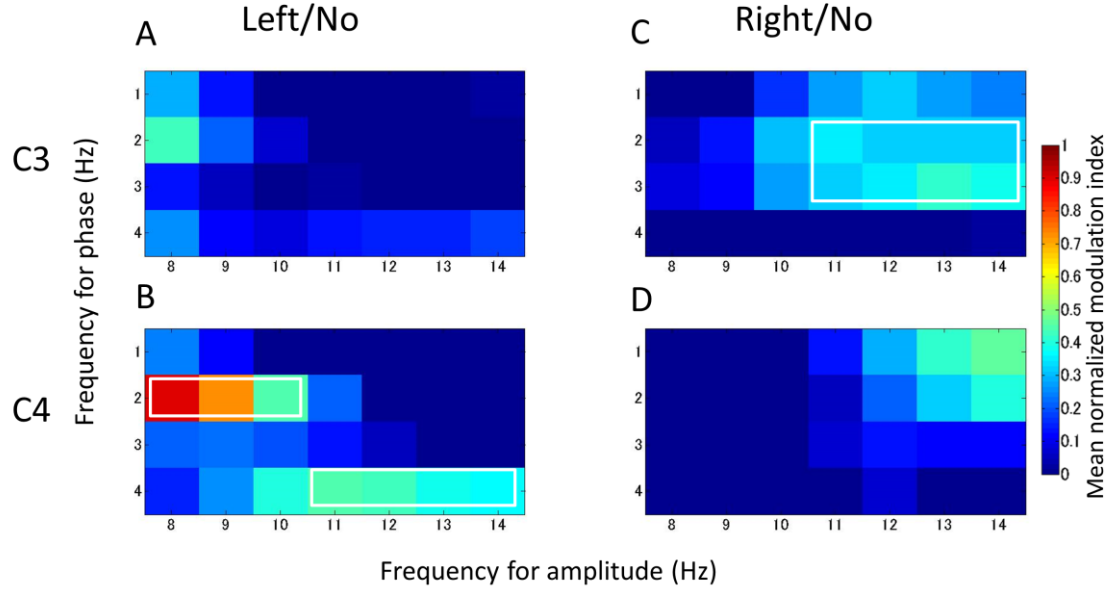


Figure 16. The difference in the modulation index for the left and right motor regions c between the active-response condition and the No condition for different combinations of phase (range, 1–4 Hz) and amplitude (range, 8–14 Hz). A: The difference in the normalized modulation index for the C3 electrode (the left motor region) during preparation in Left trials and the normalized modulation index for the same electrode during preparation in No trials. B: The difference in the normalized modulation index for the C4 (the right motor region) electrode during preparation in Left trials and the normalized modulation index for the same electrode during preparation in No trials. C: The difference in the normalized modulation index for the C3 electrode during preparation in Right trials and the normalized modulation index for the same electrode during preparation in No trials. D: The difference in the normalized modulation index for the C4 electrode during preparation in Right trials and the normalized modulation index for the same electrode during preparation in No trials. White squares indicate a significant difference between conditions ($P < 0.05$, cluster-based permutation test). Only the motor region contralateral to the side of

motor preparation exhibited a significant difference in delta-alpha normalized modulation index between the active-response and the No-response condition.

To evaluate the precise relation between phase and amplitude in the identified clusters in active-response and No conditions, we calculated the mean normalized alpha amplitude depending on delta phase. The results showed that alpha amplitude was significantly modulated with respect to delta phase ($P < 0.001$; Figure 9). The direction of modulation was positive at a delta phase of around $-\pi$ and π radians and negative at a delta phase of around 0 radians. (Figure 9). The modulation was more prominent in active-response conditions compared to No conditions.

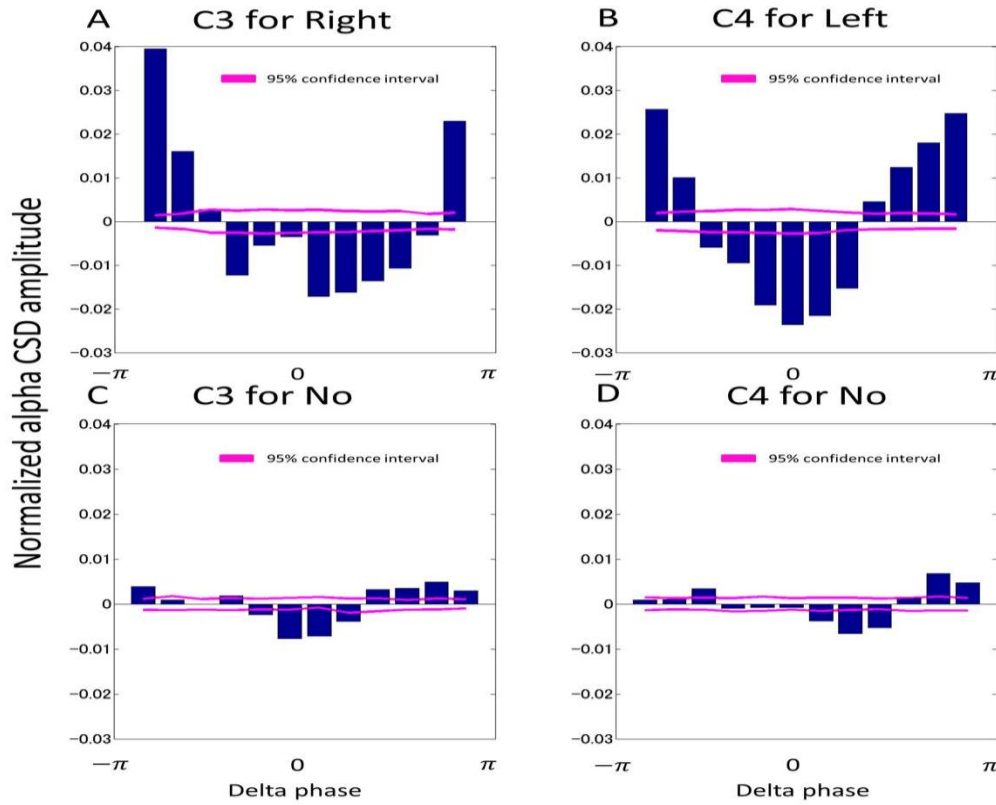


Figure 17. The current source density (CSD) amplitude at alpha frequencies according to the delta phase. The data are from the significant clusters showed in Figure 16: 2–3 Hz phase and 11–14 Hz amplitude for C3 and 2 Hz phase and 8–10 Hz amplitude and 4 Hz phase and 11–14 Hz amplitude for C4. 0 radian indicates the unpreferred delta phase for alpha amplitude. For the C3 electrode, the mean amplitude at 11–14 Hz at each time point across trials and subjects was assigned to one of 12 bins based on the 2–3 Hz phase. For the C4 electrode, the mean amplitude at 11–14 Hz at each time points across trials and subjects was assigned to one of 12 bins based on the 4 Hz phase and the mean amplitude at 8–10 Hz was assigned based to a bin based on the 2 Hz phase. A: C3 for Right trials. B: C4 for Left trials. C: C3 for No trials. D: C4 for No trials. Normalization used mean and standard deviation on a single trial basis. To generate 95% confidence interval, delta-phase and alpha-amplitude were randomly paired (surrogate data approach).

We also explored a correlation between single-trial reaction time and single-trial modulation

index of the significant frequency pairs in the contralateral motor cortex. In Left condition, modulation index between 2Hz-phase and 9-10-Hz amplitudes and 3hz and 13-14 amplitues was negatively correlated with the reaction times when the target was identical (Speaman's rho-value = -0.05 to -0.08, $p < 0.05$). All other Left/Right/No conditions did not yield significant results.

Due to the limited spatial resolution of EEG, one might dispute whether the observed synchrony was true synchrony or conduction synchrony. If the synchrony was because of volume conduction, phase difference between a pair of electrodes should be concentrated around 0 and π (Melloni et al., 2007). On the contrary to this, phase differences of the observed synchrony were distributed to other angles (supplementary Fig 1). Therefore, volume conduction can not fully explain the results. Focusing on the motor (C3/C4) and occipital regions (O1/O2) in which two distinctive alpha lateralizations were observed, the phase differences were also scattered (supplementary Fig 2). Therefore, the changes in the regions did not share a single source (*i.e.* volume conduction).

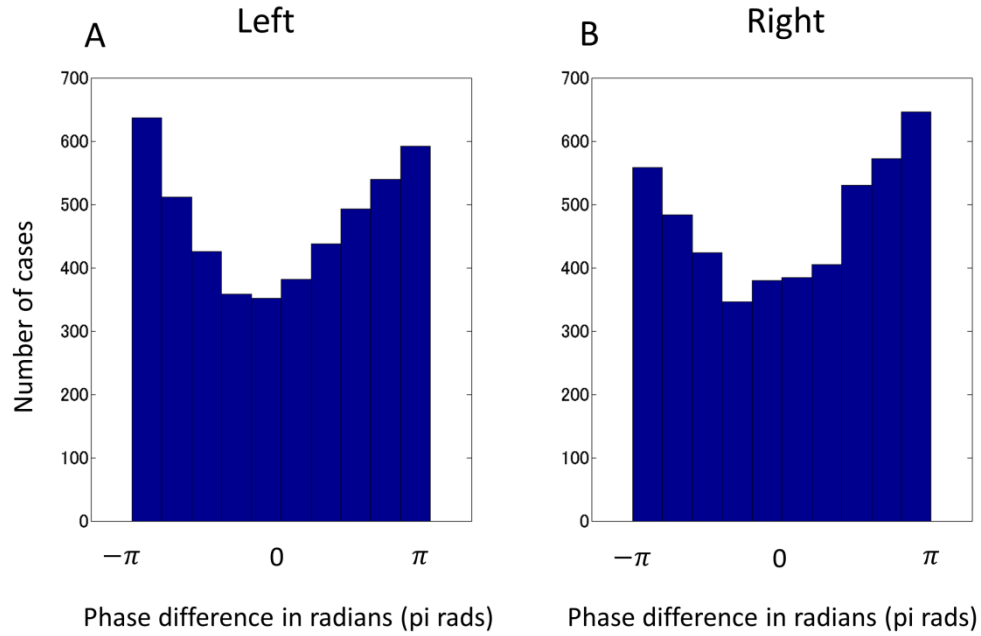


Figure 18. Distribution of phase difference between electrodes in the motor and occipital regions contralateral to the side of motor preparation 800ms after the onset of cue stimulus at 12Hz. A: Phase difference between C4 and O2 electrodes in Left condition. B: Phase difference between C3 and O1 electrodes in Right condition. These graphs illustrate that significant decreases of alpha amplitude in the motor and occipital regions are not explained by volume conduction. If the results are due to volume conduction, the distribution should be tightly around zero or pi radians. The observed distributions are spread to other radians.

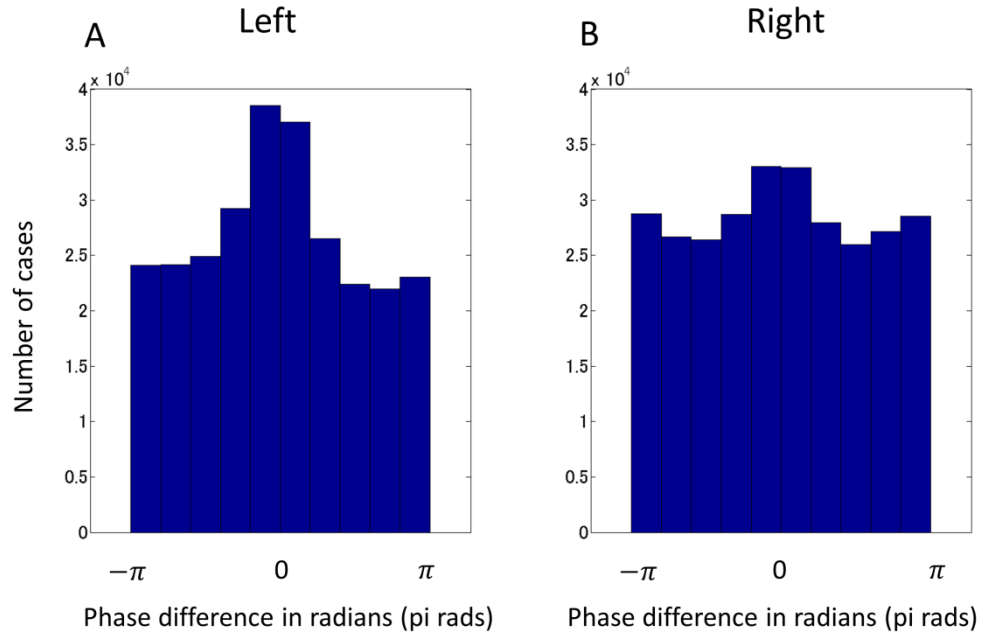


Figure 19. Distribution of phase difference between a pair of electrode (c3 and o2) 400ms after the onset of cue stimulus at 3Hz. A: Left condition. B: Right condition. These graphs illustrate that volume conduction does not account for the observed significant synchronization. If the results are due to volume conduction, the distribution should be tightly around zero or pi radians. The observed distributions are spread to other radians.

Discussion

This study investigated the EEG dynamics of motor preparation, eliminating low-level visual processing by comparing relevant conditions. The performance of subsequent motor responses differed depending on the conditions of preparation, illustrating the influence of the experimental manipulation on the motor system. For both the Left and Right conditions compared to the No condition, delta phase synchrony appeared before the decrease in alpha amplitude. Furthermore, the temporal evolution of the decrease in alpha amplitude progressed from occipital to motor regions. When comparing the Left and Right conditions, alpha lateralization was evident in the occipital and motor regions. To explore whether there was a direct relation between delta-phase synchrony and alpha-amplitude changes, we analyzed phase-amplitude coupling between delta phase and alpha amplitude in the motor regions. Phase-amplitude coupling between delta and alpha frequencies, respectively, was functionally specific. Significant coupling of delta phase and alpha amplitude was evident only in the motor cortex contralateral to the side of movement preparation, i.e., the left motor region for the Right condition and the right motor region for the Left condition. Taking into account the inhibitory role of alpha-band oscillations in the cortex, we suggest that delta-alpha phase-amplitude coupling is a mechanism by which the cortical inhibition can be adjusted, utilizing the fact that alpha oscillations have a preferred and unpreferred delta phase. This is in line with a hypothesis that lower frequency phase modulates cortical excitability, and subsequently affects local processing (Lakatos et al, 2005).

Global delta-phase synchrony

Human cognition and action require integration of information from a number of regions of the brain, and mechanisms for such integration should be postulated. For motor control, a previous study reported that a visuo-motor task produced a widespread change in event-related local field potentials (Ledberg et al., 2007). But how those regions relevant for the visuo-motor task interact with each other has remained unknown. Phase synchrony has been postulated as a putative mechanism for communicating information

between neural populations (Varela et al., 2001). Synchrony in different bands has been implicated in variety of functions. Large-scale gamma synchrony plays a role in conscious perception and attention (Melloni et al., 2007; Doesburg et al., 2008), beta synchrony mediates the maintenance of status quo (Engel and Fries, 2010), alpha synchrony plays a role in consciousness (Palva and Palva, 2007), and theta synchrony is critical in memory (Uhlhaas et al., 2010; Kawasaki et al., 2014). To our knowledge, the current study is the first to identify global synchronized networks at delta-band frequencies that correspond to motor control (Figure 14), whilst minimizing the effects of volume conduction by CSD transformation. Recent studies showed that delta activity mediated attentional selection (Lakatos et al., 2008), and stimulus expectation (Arnal and Giraud, 2013). More relevant to our study, the phase of slower oscillations, including those in the delta frequency band, reflects sensory selection (Schroeder and Lakatos, 2009). Hence, our results pertaining to delta-phase synchrony could also be relevant to the transfer of sensory information.

Furthermore, we should note that global phase synchrony appeared only in the delta band. Synchrony in the delta band may be particularly suited to mediate communication in the motor system, as distant neuronal groups favor lower frequency synchronization to interact (Buzsáki, 2009). Oscillations with different frequencies have varying temporal windows for computation (von Stein et al., 2000). As a result, they are associated with different spatial magnitudes. This means that faster oscillations have narrower spatial scales, and slower oscillations can reach far broader regions (Buzsáki, 2009). Taken together with our results, this suggests that global interactions mediated by delta-band synchrony influence the amplitude of alpha-band oscillations in the motor cortex by the phase-amplitude coupling.

Alpha lateralization in the motor and occipital regions and travelling alpha

We observed functionally specific alpha modulation after the global phase synchrony in the delta band, namely alpha lateralization (Figure 11, 12, and 13). Alpha lateralization is a phenomenon in which

alpha-band amplitude is reduced in the contralateral hemisphere and increased in the ipsilateral hemisphere in relation to the motor, visual, and somatosensory systems involved in the task (Pfurtscheller et al, 2000; Worden et al., 2000; Haegens et al., 2011). The mechanism underlying this reduction may be a change in cortical inhibition (Klimesch et al., 2007). Our study, in line with previous research (Arroyo et al., 1993; Pfurtscheller and Andrew, 1999), showed that the motor cortex contralateral to the response-preparing hand was more released from inhibition than the ipsilateral motor cortex. The novel result from our study is that alpha lateralization was also observed in the occipital cortex. Occipital alpha lateralization has been previously associated with a shift of spatial attention (Thut et al, 2006; Gould et al., 2011). However, given that these effects were induced by a visual stimulus that had no explicit directional information (right or left) for spatial attention, we argue that this represents a proximal link between motor preparation and spatial attention.

There has been debate as to whether spatial attention is a supramodal mechanism (Posner and Dehaene, 1994) or an emergent property originating from the activation of sensorimotor circuits (Desimone and Duncan, 1995; Rizzolatti et al., 1987). The latter proponents showed proximal links between overt eye movements and covert spatial attention in oculomotor control (Hoffman and Subramaniam, 1995; Katnani and Gandhi, 2013). If spatial attention relies on the same neural circuit for movements, movements themselves should induce the shift of spatial attention (Rizzolatti et al., 1987; Smith and Schenk, 2012). Our paradigm, in which limb responses were made without eye movements and the stimuli did not have any directional information, enabled us to test this hypothesis, and our results suggest that motor preparation and spatial attention are indeed hard to separate, if not impossible.

In addition, the decrease in alpha-band amplitude was observed with a temporal order from the occipital to motor regions in Right/No and Left/No comparisons. The movement of the modulation of alpha-band amplitude reflects the direction of communication and is called travelling alpha (Nunez et al., 2001; Sauseng et al., 2005; Klimesch et al., 2007) . Given that the Right/No and Left/No comparisons

required a sensorimotor transformation, the travelling alpha observed in the current study is likely to reflect this sensorimotor transformation.

Phase-amplitude coupling between delta and alpha frequencies

We observed functionally specific cross-frequency coupling between delta phase and alpha amplitude in the motor regions. Only the cortex contralateral to the side of motor preparation exhibited an increase in phase-amplitude coupling relative to the No condition (Figures 8 and 9). All couplings between delta phase and alpha amplitude were significant for the Left and Right conditions assuming Gaussian distribution. Cross-frequency coupling is a mechanism to integrate fast local computations with slow global computations (Canolty and Knight, 2010). In line with this, alpha amplitude in the motor regions (fast local computations) were coupled with delta-phase activities which represented global synchrony and preceded the change in the amplitude of alpha oscillations/synchrony. In other words, the phase-amplitude coupling relayed information through delta-synchrony to local computations made by alpha amplitude. In previous literature, theta-gamma phase-amplitude coupling has been reported across many cortical regions of the human brain (Canolty et al., 2006). The physiological mechanism could be an increased generation of stimulus-driven spikes that occurs due to a change in cortical excitability (Fries, 2005). By contrast, our results showed that alpha amplitude, which actively inhibits local computation (Klimesch et al., 2007), was coupled with delta-phase. To examine the precise role of phase-amplitude coupling it is necessary to explore how delta phase and alpha amplitude are coupled. The modulation index did not provide any useful information on this topic. However, the mean alpha amplitude at a specific delta phase revealed a detailed relation between phase and amplitude. Interestingly, positivity and negativity of alpha amplitude depended on delta phase. In other words, alpha amplitude had an unpreferred phase as well as a preferred phase. The fact that alpha amplitude decreased with time indicates that the coupling on the unpreferred phase was stronger than that on the preferred

phase. Therefore, we argue that delta-alpha phase-amplitude coupling works to release cortical areas from inhibition by down-regulating alpha-amplitude in an unpreferred delta-phase, given that alpha amplitude reflects the degree of cortical inhibition (Klimesch et al., 2007).

In summary, we explored the neural dynamics of motor control and showed that global delta-phase synchrony preceded a functionally relevant decrease in local alpha amplitude. Crucially, delta-alpha phase-amplitude coupling appeared in a functionally specific manner to connect slow global computation with fast local computations.

Chapter 3

Introduction

Adjusting neural computation to external stimuli would be crucial for the efficiency. Prediction of the stimuli indeed improves stimulus processing, allocation of attention and behavioral performance (Correa et al., 2005; Arnal et al., 2014). If stimuli have rhythmic structures, prediction becomes easier. The brain creates an internal model in which temporal regularities are stored to predict what will happen in the future (Arnal et al., 2014). Especially, the brain is automatically tuned to such temporal regularities when recruiting the motor system (Schubotz et al., 2000; Grahn and Brett 2007; Bengtsson et al. 2009; Teki et al. 2011). The motor system simulates an appropriate movement before it to be synchronized with events in the future, in order to improve performance including the timing of a response (Schubotz 2007; Tian and Poeppel 2010; Arnal and Giraud 2012). Put it more precisely, corollary discharges, namely forward prediction of movements, spread to other sensory areas to modulate sensory activities. Specifically, beta oscillation, which is known to be involved in the initiation of movements, contributes to the underlying mechanism (Pfurtscheller, 1999; Donner et al. 2009; Fujioka et al. 2012; de Lange et al. 2013). Such sensory-motor integration requires combining computation of external stimuli and internal motor process, which often have very different time scales (van Atteveldt et al., 2014). Previous studies suggested that phase activity of lower frequency neural oscillation could be the mediating mechanism to connect those different computation (Ivry and Schlerf 2008; Morillon et al., 2009; Kajihara et al., 2015). Neural excitability, which is reflected in the phase of lower frequency oscillation, adjusts itself to sensory events often with attentional bias or expectation (Schroeder and Lakatos 2009; Arnal and Giraud, 2012). This entrainment mechanism facilitates decision-making process including reaction time (Lakatos et al., 2008; Stefanics et al., 2010; Wyart et al. 2012; Cravo et al. 2013). Therefore, in a sensory-motor task where prediction of stimuli is possible, lower frequency oscillations entrained by external stimuli exert temporal control on the activity of motor system for it to execute at the right timing. For this mechanism, we

hypothesized that delta-beta phase amplitude coupling is a candidate. In order to test the hypothesis, we conducted a novel-tapping task with music. Comparing tapping with music and tapping without music conditions, our hypothesis is that delta-beta phase-amplitude coupling would exhibit stronger modulation in the tapping with music condition, since motor process must be integrated with external sensory events in the condition alone. Crucially, we also resorted to investigate the entrainment of lower-frequency neural oscillation by external rhythmic events, which were music in this context, to clarify a neural mechanism to extract temporal regularities in a stimulus.

Material and methods

Participants

Sixteen healthy participants (10 males & 6 females, 20–29 years old, right-handed) were tested in this study. Recorded data of two participants were too noisy because of their movements during the experiment so that they were excluded from further data analysis. Before the experiment, all participants were given informed consent. The study was approved by the RIKEN ethics committee. All participants had normal or corrected-to-normal vision and no neurological or psychiatric disorders.

Experimental paradigm and Procedure

Participants were instructed to perform tapping freely with music (Music Tap condition), tapping freely without music (Tap condition) by the right hand, and listening to music without tapping (Music Listen condition). There was no instruction as to how they should tap in any condition. A 17-inch CRT monitor (CPD-E220, SONY, Japan; 100 Hz refresh rate) was placed 100 cm away from participants. Participants seated in a chair maintained their head position with a chin rest and fixated on a central dot throughout the experiment. ‘Music Tap’, ‘Tap’ and ‘Listen’ conditions contained two trials and each lasted for 3 minutes. Trials were randomly presented. ‘Born this way’ by Lady GAGA was used for the musical stimulus. After each trial, participants were allowed to have a rest as long as they wished.

EEG recording

The same EEG recording procedure used in Chapter 2 was applied to this experiment.

EEG data preprocessing

Trials with artifact-free EEG data were segmented into 1.0-s epochs from 500 ms before to 500 ms after each tapping. We applied current source density (CSD) transformation. Its details were already described in chapter 2.

Stimulus preprocessing

Musical stimuli were first bandpass-filtered from 0.1 to 10000 Hz. Then Fourier transform was applied to derive its power spectrum. The peak power was located at 2.0661 Hz. We reasoned that this frequency would be most recognizable by the participants. Therefore their brain would be entrained by that. For EEG data analysis, 2Hz oscillation was substituted by 2.0661Hz.

EEG processing

Wavelet analysis

Instantaneous amplitude and phase were computed using complex Morlet wavelet function. The detail was written in Chapter 2.

Phase locking factor (PLF)

The PLF (Tallon-Baudry et al., 1999) is a similar measure to PLV described in Chapter 2, but slightly differs since it quantifies stability of phase activity at given time across trials in one electrode. For electrode i at time t , PLF is calculated as;

$$PLF_i(t) = \left| \sum_{n=1}^N \exp(j(\theta(t, n))) \right|$$

where N is the number of trials, j is an imaginary unit, and $\theta(t, n)$ is the instantaneous phase in trial n at

time t . The derived quantity (range, 0–1) represents the degree of phase stability across trials with the maximum signifying complete phase stability.

Modulation index

Modulation index proposed by Canolty et al. (2006) was utilized to quantify the degree of phase-amplitude coupling. The index was calculated based on data from electrodes C3 and C4, which were located over the motor region of the left and right hemisphere, respectively. The detail of the index including normalization process was already described in Chapter 2. In the current study, the index was calculated over the time window from -500 to 500ms around each tapping event by averaging the instantaneous values. The calculated index was averaged again across trials for each subject.

Stimulus brain phase locking value

The bandpass-filtered musical stimulus with 0.1 – 10000Hz was first subject to Hilbert transform to derive the complex-valued signals from which we extracted instantaneous amplitude. Then, the second wavelet transform applied to the amplitude series to extract the envelope, or phase activity of 2.0661Hz. This phase activity of amplitude was compared to the corresponding 2.0661Hz phase activity of the brain recorded by the electrodes, to explore synchronization between them. For the quantification, we used PLV explained in chapter 2, which described the magnitude of consistency in phase difference. These procedures were applied to Music Tap and Music Listen conditions. PLV was calculated 500ms before and after each tapping event for Music Tap condition. For Music Listen condition, the time point corresponding to the tapping events in Music Tap condition was used to calculate PLV. A hypothesis to be tested was that in comparison with Music Listen condition, Music Tap condition, in which temporal regularities of music should be strongly aware of since sensory motor integration is required, would yield significantly higher PLV value, which reflected stronger stimulus brain synchronization.

Result

Behavioural performance

The average performance of inter-tap interval in Music Tap and Tap conditions were an RT of 571.7 ms with a SD of 229.9 ms and an RT of 751.3 ms with a SD of 369.4 ms respectively.

Amplitude difference between Music Tap and Tap conditions

Amplitude of C3 and C4 (the contralateral/ipsilateral motor cortex) between Music Tap and Tap conditions were compared. There was no significant difference in amplitude between Music Tap and Tap conditions for C3 and C4 (permutation test, *n.s*) (Figure 20). This result would eliminate the possibility that the difference in phase amplitude coupling between the conditions is due to amplitude difference.

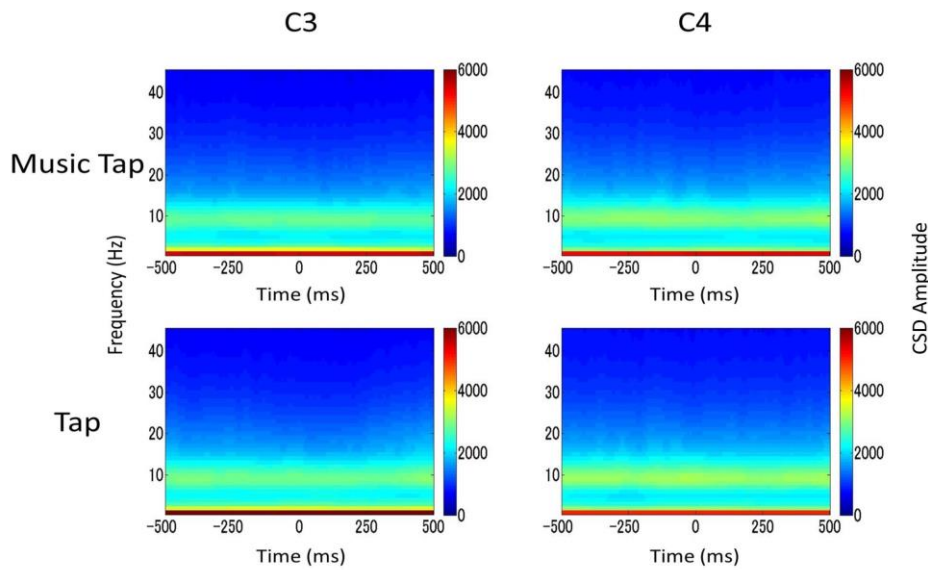


Figure 20. Subject-averaged CSD amplitude of C3 and C4 in Music Tap and Tap conditions. 0 ms signifies the time point where a tapping occurred. Comparison of C3 in CSD amplitude between the conditions did not produce any significant difference. Also, comparison of C4 in CSD amplitude between the conditions did not produce any significant difference.

PLF difference between Music Tap conditions and Tap condition

PLF differences between Music Tap and Tap conditions in C3 and C4 electrodes were investigated. Only in C3 electrode, PLF in Music Tap condition was significantly higher than in Tap condition (Cluster-based permutation test, $p < .05$). The significant PLF events in C3 happened before and after tapping for delta (1-4 Hz) band (Figure 21). 2Hz signified 2.0661 Hz.

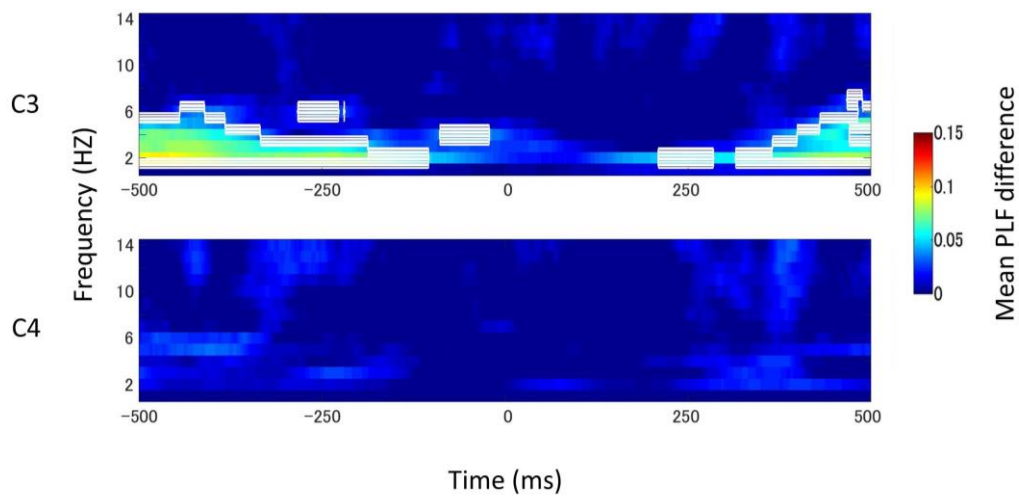


Figure 21. Subject-averaged PLF difference between Music Tap and Tap condition in C3 and C4 electrodes. 0 ms signifies when subjects tapped by their right hand. 2Hz was computed as 2.0661Hz. White line indicates significant time-frequency window.

PLF difference between Music Tap conditions and Music Listen condition

PLF difference between Music Tap and Music Listen conditions in C3 and C4 electrodes was investigated. PLF Only in C3 electrode, PLF in Music Tap condition was significantly higher than in Music Listen condition (Cluster-based permutation test, $p < .05$). Significant PLF events in C3 was observed throughout the period for delta (1-4 Hz) band (Figure 22). 2Hz signified 2.0661 Hz.

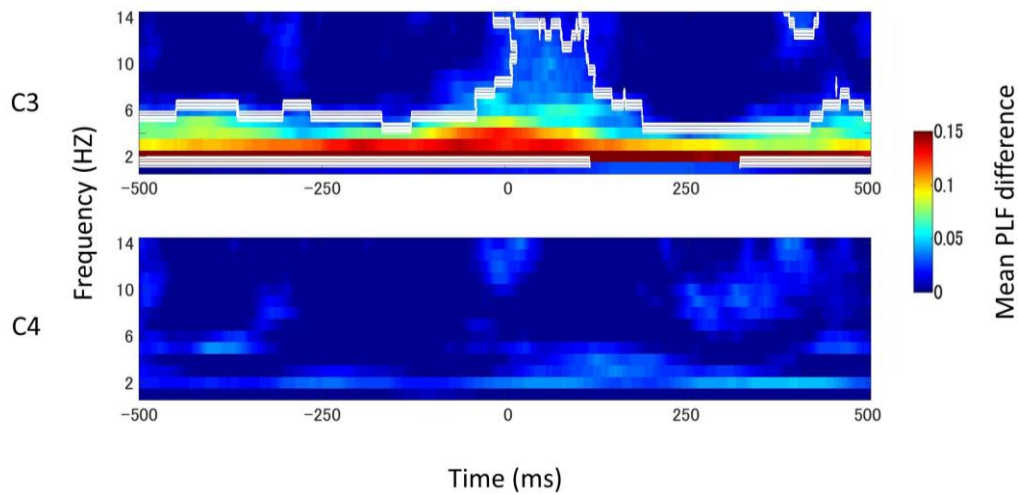


Figure 22. Subject-averaged PLF difference between Music Tap and Music Listen condition in C3 and C4 electrodes. 0 ms signifies when subjects tapped by their right hand. 2Hz was computed as 2.0661Hz. White line indicates significant time-frequency window.

Synchronization between musical stimulus and brain response

To clarify our hypothesis that phase activity in the brain would be more entrained to the peak frequency of musical stimuli when sensory motor integration was in demand, stimulus-brain synchronization was investigated using PLV. Comparing Music Tap and Music Listen conditions, Music Tap condition showed significantly higher 2.0661Hz synchronization between music stimulus and brain responses in

comparison to Music Listen condition (permutation test, $p < .05$) (Figure 23).

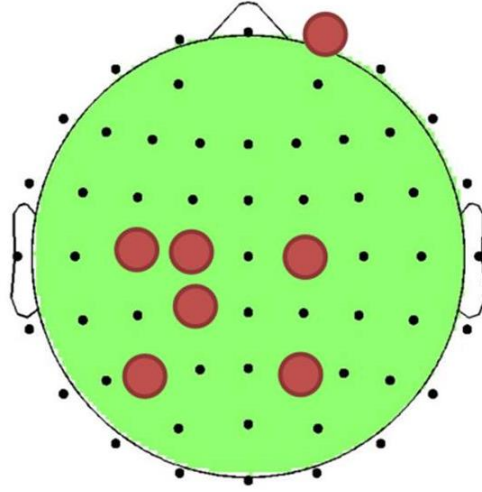


Figure 23. Stimulus brain phase locking value at 2.0661Hz. Red colored electrodes showed significantly higher PLV in Music Tap conditions, in comparison with Music Listen condition (permutation test, $p < 0.05$).

Cross-frequency coupling in the motor regions

To investigate whether delta-beta phase amplitude coupling reflects sensorimotor integration, we calculated normalized modulation index between 1-4 Hz phase (2.0661Hz for 2Hz) and 8-45 Hz amplitude. A cluster-based permutation test for normalized modulation index was applied to Music Tap and Tap comparison for data recorded from C3 and C4. The significant frequency pairs were between 2.0661 Hz phase and 18 - 24 Hz, 5 Hz phase and 15 - 24 Hz amplitude in C3 electrode, 5 Hz phase and 17 - 22 Hz amplitude in C4 electrode (cluster-based permutation test with Bonferroni-correction, $p < 0.001$) (Figure 24).

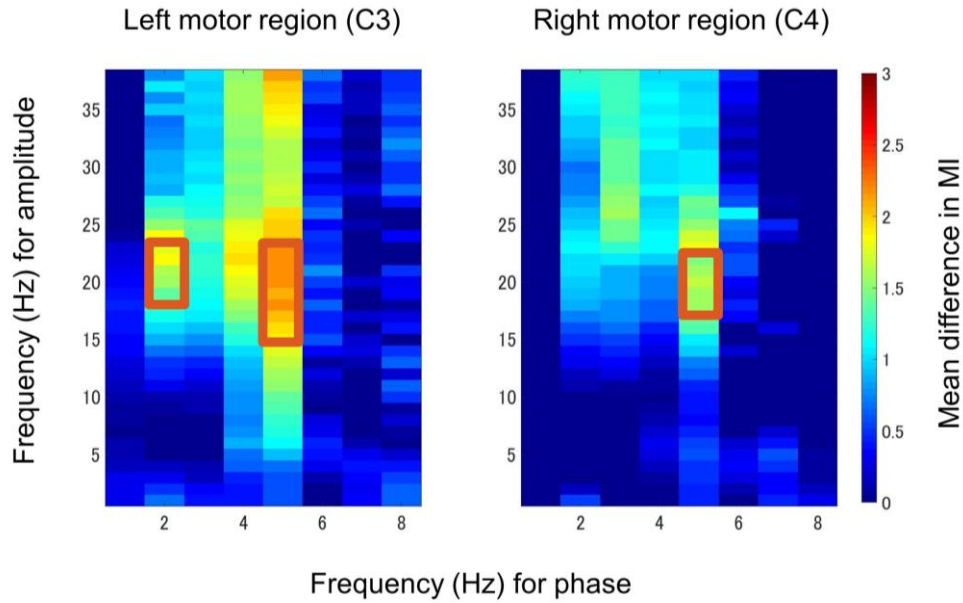


Figure 24. Mean difference of normalized modulation index between Music Tap and Tap conditions in C3 and C4. 2.0661 Hz phase and 18 - 24 Hz, 5 Hz phase and 15 – 24 Hz amplitude in C3 electrode, 5 Hz phase and 17 – 22 Hz amplitude in C4 electrode are identified as significant clusters. Red line indicates significance (cluster-based permutation test with Bonferroni-correction, $p < 0.001$)

Discussion

We observed that delta PLF and delta-beta phase amplitude coupling in the contralateral motor cortex were stronger in Music Tap condition compared to Tap condition, suggesting that delta phase was modulated consistently across trials to tap at the appropriate timing and the phase amplitude coupling was the mechanism to support sensory-motor integration. Furthermore, the peak-frequency of the musical stimulus, 2.0661Hz, had higher stimulus-brain synchronization in Music Tap condition in comparison with Music Listen condition, indicating that the brain uses the synchronization to extract temporal regularities of a stimulus.

Delta entrainment to music stimulus

Our brain is a prediction machine. It predicts ‘what’ and ‘when’ simultaneously (Arnal and

Giraud, 2012). Regarding ‘When’ information, temporal regularities are ubiquitous in our world. Namely, events are periodic and predictable. Hence, if there is an appropriate mechanism in the brain, which enables prediction, we could achieve computation that is more efficient. In order to understand such a mechanism in the brain, a theory of predictive coding would be helpful. Predictive coding is the application of Bayesian framework to the brain (Friston 2005; Bastos et al. 2012). It proposes that our brain constantly estimates the causes of future sensory events, and the estimates are evaluated with respect to the actual events (Friston, 2005; Knill and Pouget, 2004; Kleinschmidt et al., 2002). Prediction error, which is the difference between the estimates and the sensory inputs, propagates to relevant regions to adjust the prediction. However, predictive coding mainly explains a mechanism about estimating ‘what’. Arnal and Giraud (2012) extends this framework to suggest a possible principle to infer ‘when’ information. This is coined as predictive timing. Predictive timing (temporal expectation) is a theory that the brain internalizes and updates temporal regularities and contingency of sensory events in order to estimate the temporal occurrence of future events (Nobre et al., 2007; Andreou et al., 2011; Jones et al., 2002). In our experimental paradigm, participants had to extract the rhythmic structure to tap with musical stimuli. We argue that the mechanism responsible for that is predictive timing.

Predictive timing should be supported by a variety of oscillations since stimuli with different rhythms are available in the world. A notable example is speech. Speech has various rhythmic components with different frequencies: syllable, word, prosody, and so on. Different frequency activities in the brain could be entrained to each component of speech (Giraud and Poeppel, 2012). Prediction by appropriate rhythm enables economy of metabolism, since neural populations only have to be active at the right timing. In other words, predictive timing is a mechanism for selective computation at temporal scale. Neurophysiological explanation of the theory is that delta-theta (2-8 Hz) oscillation adjusts its phase by phase resetting before a relevant event to happen (Schroeder and Lakatos, 2009; van Atteveldt et al., 2014). Alternative explanation is that delta-phase activity accumulates temporal information. Namely,

the phase activity tracks how long have elapsed since the occurrence of a certain event (Arnal et al., 2014). Our PLF result could endorse the former phase resetting hypothesis since PLF means the consistency of phase across trials.

Music performance often involves playing with other instruments in tempo. This requires the extraction of temporal regularities from other musical parts. Our paradigm could be considered as quasi music performance, since subjects needed to tap in tempo with music. We argue that using delta phase activity, subjects tracked one beat to another in the stimulus. Stronger delta PLF in Music Tap condition, which indicates systematic modulation of delta phase, would be a manifest of that mechanism. This mechanism would enable the sensory-motor coordination in strict temporal windows. The entrainment would physiologically mean the alignment of cortical excitability. When events happen, cortical excitability should be the highest to facilitate the processing (Lakatos et al., 2008; Stefanics 2010). In support of this, neural responses heighten immediately before predictable events to happen, whilst the responses are reduced for other time window (Costa-Faidella et al., 2011; Zhang et al., 2009). On the other hand, when stimuli are unpredictable or a person does not yet extract the temporal regularities, the brain increases the rate of spikes, raising the level of neural responses continuously. In LFP signal, gamma band activity reflected this high level of neural responses (Ghitza and Greenberg, 2009). Once it becomes predictable, the computation shifts to phase activity of lower frequency (Arnal and Giraud 2012).

It should be noted that prediction or expectation of periodic events is not the same with attention. Over all, attention increases neural responses, whilst expectation reduces the responses to the known stimuli (Arnal and Giraud, 2012; Wyart et al., 2012; Summerfield and Egner, 2009). Attention emphasizes certain stimuli over the others to increase the corresponding neural responses. On the other hand, expectation economizes neural responses using prior probability.

Stimulus brain synchronization

Auditory cortex responds to the amplitude and frequency of auditory information (Giraud and Poeppel, 2012). As phase tracks speech envelope (Henry and Obleser, 2012; Stefanics et al., 2010; Neuling et al., 2012; Ng et al., 2012), we reasoned that phase activity in the brain tracks envelope of the musical stimulus. In speech, when envelope tracking went wrong, subjects had difficulty in the understanding (Golumbic et al., 2013). Filtering speech by envelope manipulation, theta phase could not follow the envelope and speech recognition failed (Henry and Obleser, 2012). Multiple rhythmic stimuli exist in the world they can entrain multiple oscillations in the brain at the same time (Gross et al., 2013). In the previous studies, sources, which generates the rhythms entrained to the stimuli, are located in the auditory cortex (Henry et al., 2014; Herrman et al., 2013; Besle et al., 2011). Moreover, entrainment of rhythms in the auditory cortex is structured hierarchically such that higher-level auditory regions respond preferentially to slower rhythms (Giraud et al., 2000). In our paradigm, we found that slower rhythm in the brain was entrained to the external stimuli. This would signify that high-level auditory cortical regions were entrained by the stimuli. However, limited spatial information of EEG hinders us from concluding where the sources are.

Delta beta phase-amplitude coupling

Delta beta phase-amplitude coupling in the contralateral motor cortex was stronger in Music Tap condition in comparison with Tap condition. Normalized modulation index, which we used to quantify phase-amplitude coupling, standardized the magnitude of amplitude. Therefore, the significant difference signifies that beta amplitude systematically modulates at some phase of delta oscillation.

In this study, rhythmic structures of the stimuli would first be detected by delta phase activity in the auditory cortex. The region then sends a modulatory signal, which adjusts cortical excitability to

raise the probability of spike generation, to the motor cortex for it to activate at the right timing. Such cross-modal modulatory signals pass through thalamus (Schroeder and Lakatos, 2009; Schroeder et al., 2008) or direct cortico-cortical pathway (Besle et al., 2008; Arnal et al., 2009). Receiving the modulatory signals from the auditory cortex, the motor cortex fluctuates its cortical excitability at delta-theta frequency (Atteveldt et al., 2014). The up and down of cortical excitability would selectively reduce and increase beta amplitude at the right timing. Prior to and in the execution of movements, beta amplitude decreases whilst after the execution the amplitude increased more than the baseline and recovered to the baseline (Baker et al., 2001; Pfurtscheller and Lopes Da Silva, 1999). Along with alpha rhythm, beta rhythm would reflect the increase and decrease of cortical excitability as well (Pfurtscheller, 2003). Given delta phase activity signifies cortical excitability, the brain has cortical excitabilities with different temporal scales. This hierarchical cortical excitability could be the underlying mechanism of the phase amplitude coupling in the motor cortex.

Another interpretation of beta band activity in the current paradigm is the involvement in prediction. Prediction is not only associated with lower frequency phase but also with alpha (8-12 Hz) and beta (13-30 Hz) bands. Reduction in power of alpha band has been observed when expected stimuli were presented (Rohenkohl et al., 2011; Thut et al., 2006). Furthermore, the phase of alpha oscillation adjusted itself with temporally unpredictable stimuli (Scheeringa et al., 2011; Busch et al., 2009). Interestingly, the motor system per se is involved in the perception of elapsed time at the time scale of seconds (Ivry and Schlerf 2008; Morillon et al. 2009). Specifically, motor simulation allows one to evaluate time elapsed by converting the time elapsed to simulate the trajectory of given movements. Given this argument, not only delta but also beta activity in the observed delta-beta phase amplitude coupling could contribute to the perception of the rhythmic structures.

Interestingly, beta band modulates not only in the auditory cortex but also the motor cortex in relation to auditory information (Fujioka et al., 2009, 2012). Indeed the motor system is also involved in

rhythm perception (Saleh et al., 2010; Fujioka et al., 2012) and sends signals to the auditory cortex to align ongoing oscillations to synchronize activities (Nelson et al., 2013). Furthermore, accurate perception of rhythm relies on the balance of beta amplitude in the auditory and motor regions; higher beta amplitude in the auditory cortex and lower beta amplitude in the motor cortex (Fujioka et al., 2012). Taken together, beat perception could be processed in the sensory-motor loop, instead of the sensory system alone (Arnal et al., 2014). Our delta-beta phase amplitude coupling could reflect parts of this mechanism.

Chapter 4

Introduction

Mammalian cortex has a laminar structure. Cortical column has roughly six layers based on cytoarchitecture (Kandel et al., 2000), and there is communication between the layers. However, the principle underlying such communication remains still unclear. Several studies have suggested that phase-amplitude coupling between LFP oscillatory activities in the different layers are the underlying mechanism (Spaak et al., 2012; Giraud and Poeppel, 2012). For instance, in the visual cortex of macaque monkey rhesus, gamma activity in the granular and superficial layers co-varied with alpha activity in deeper layers (Uddin et al., 2010; Spaak et al., 2012). As cognitive function modulates alpha activity (Thut et al., 2009; Klimech, 2007), the inter-layer coupling between alpha and gamma oscillations may subserve to influence lower level sensory processing by gamma oscillation (Spaak et al., 2012). In addition to it, things are more complicated taking into an account that dominant oscillations and their functional roles differ depending on brain regions. Naturally, there could be other types of cross-frequency coupling in regions other than the visual cortex. Recently we discovered delta-alpha coupling in the motor regions of human subjects (Kajihara et al., 2015). Being inspired by above-mentioned studies, we surmised that delta-alpha couplings would turn out to be inter-layer oscillatory coupling, if they are investigated with sufficient spatial resolution. However, EEG, which we used in the two studies, could not provide such detailed spatial information in any way. , LFP oscillation could modulate spiking activities systematically changing excitability rhythmically. This enables more efficient computation by making spike events more probable when they are required (Atteveldt et al., 2014). Such modulation also could happen through inter-layer communication (Giraud and Peoppel., 2012). To authors' knowledge, no study yet has shown the inter-layer relationship clearly. Therefore, to illustrate inter-layer LFP oscillatory coupling and inter-layer LFP oscillation-spike coupling, we resorted to carry out monkey studies, in which inserting electrodes directly into the brain of monkey could give

meaningful insights into laminar-interplay of neural computation. As monkey research takes much more time to complete an experiment, I will hereby present preliminary results of inter-layer coupling of neural oscillation, which have been derived from spontaneous activity in the prefrontal cortex of monkey.

Material and methods

Subject and recording

One healthy adult male monkey had an implanted electrode with an eight-contact electrode in the prefrontal cortex. The electrode had 200 μ m inter-contact space vertically. Laminar local field potential (LFP), and multi-unit activity (MUA) were sampled with 20000Hz and recorded for 30 minutes in 6 experimental sessions. During the experiment, awake and spontaneous activity from the dorsolateral prefrontal cortex was collected. All aspects of the experimental procedure were approved by the ethics committee of Tamagawa University.

Offline analysis

Spike events were extracted from rectified MUA activity, thresholding the signal with 0.025mv (Panagiotaropoulos et al., 2012). LFP data was digitized at 1000Hz in offline processing. Computation of 1-170Hz instantaneous phase and amplitude of LFP using wavelet transform (nco = 3) was detailed elsewhere (Chapter 3 and 4). In order to reduce volume-conducted potentials, we used current source density (CSD), which was the second-order spatial derivative of LFP signals.

$$\text{CSD}(t, i) = \varphi(t, i - 1) + \varphi(t, i + 1) - 2 * \varphi(t, i)$$

where $\varphi(t, k)$ is the voltage recorded from electrode i at time t . Electrode 1 and 8 are not able to have CSD, therefore, those electrodes were excluded from further analysis. To reveal detailed co-modulation of lower-frequency phase and higher-frequency amplitude, and lower-frequency phase and spiking activities, the current experiment visualized time-frequency activity of higher-frequency amplitude from all

electrodes locked to phase trough of alpha-band (8-13Hz) oscillation from one electrode as well as time-series of spike events from all electrodes locked to the phase trough from one electrode. Alpha-phase trough was identified as local minima of the signal band-pass filtered with 8-13Hz. Amongst them, phase trough with the voltage below 30th percentile rank in each experimental session was further analysed for visualizing inter-layer phase-amplitude and phase-spike couplings. After identifying the phase trough, instantaneous amplitude and spike events 500ms before and after the phase trough were superpositioned and transformed to z-score using its temporal mean and standard deviation.

Result

Alpha Gamma amplitude coupling

Here time-frequency plot of amplitude from electrode 2, 3, 4, 5, 6, and 7, locked to the trough of alpha (8-13 Hz) phase of electrode 4 is described. Electrode 4, 5, 6 and 7 showed rhythmic modulation of gamma (>30Hz) amplitude with alpha phase. Specifically, phase trough was associated with the higher amplitude.

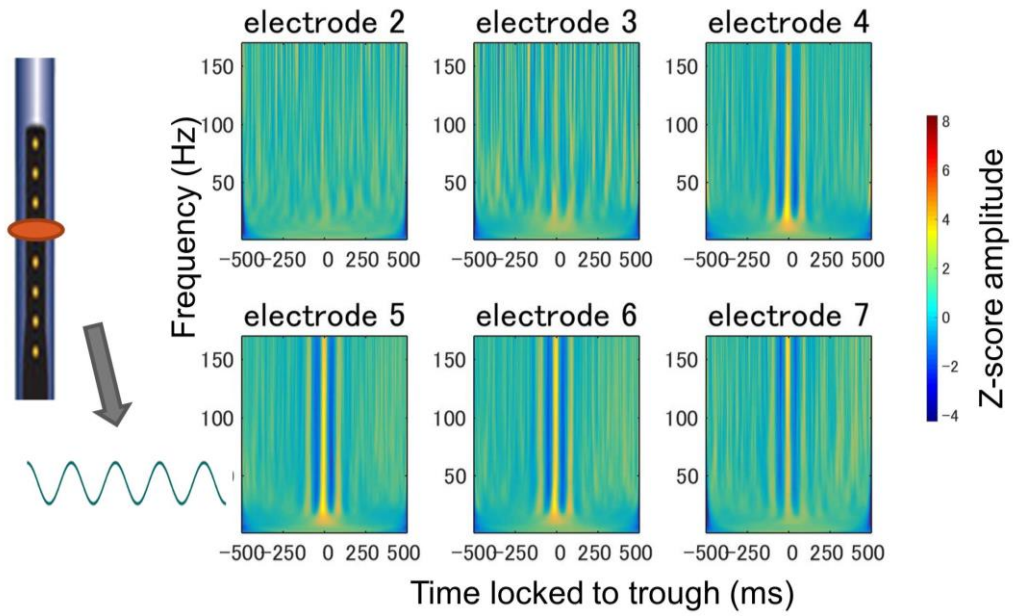


Figure 25. Time-frequency plot of amplitude in electrode 2, 3, 4, 5, 6, and 7. When locked to the trough of alpha activity in electrode 4, amplitude time-series of electrode 4, 5, 6 and 7 showed clear coupling. Higher amplitude is associated with the phase trough. Since electrode 1 and 8 could not yield CSD values because of lack of reference electrodes above and below, the electrodes were omitted from the analysis.

Here time-frequency plot of amplitude from electrode 2, 3, 4, 5, 6, and 7, locked to the trough of alpha (8-13 Hz) phase of electrode 5 is described. Electrode 4, 5, 6 and 7 showed rhythmic modulation of gamma (>30Hz) amplitude with alpha phase. Specifically, phase trough was associated with the lower amplitude.

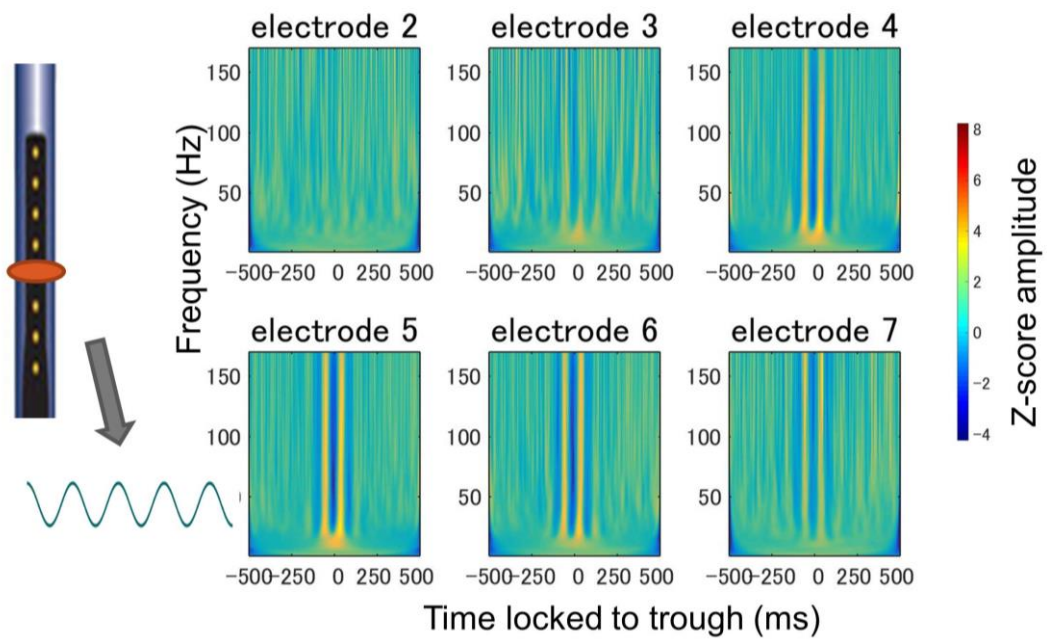


Figure 26. Time-frequency plot of amplitude in electrode 2, 3, 4, 5, 6, and 7. When locked to the trough of alpha activity in electrode 5, amplitude time-series of electrode 4, 5, 6 and 7 showed clear coupling. Lower amplitude is associated with the phase trough. Since electrode 1 and 8 could not yield CSD values because of lack of reference electrodes above and below, the electrodes were omitted from the analysis.

Alpha-phase and spike coupling

When spiking activities were locked to alpha-phase trough of electrode 4, electrode 5 and 6 have systematic spike modulation. Specifically, phase-trough of alpha activity was associated with the increase of spike incidents.

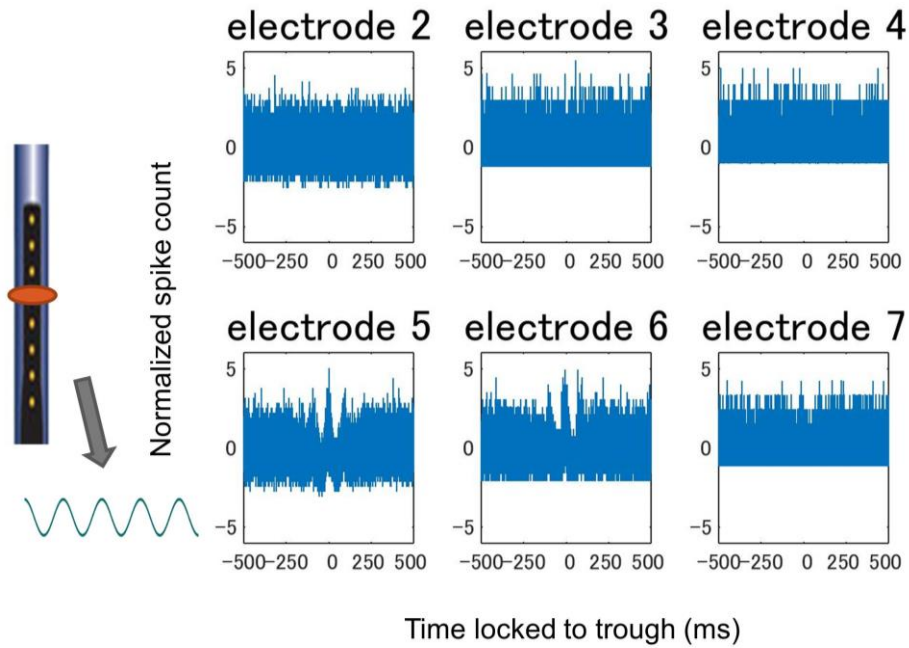


Figure 27. Plot of spike time-series in electrode 2, 3, 4, 5, 6, and 7. When locked to the trough of alpha activity in electrode 4, spiking activities in electrode 5 and 6 showed clear coupling. The phase trough was associated with the increase of spike incidents.

When spiking activities were locked to alpha-phase trough of electrode 5, electrode 5 and 6 had systematic spike modulation. Specifically, phase-trough of alpha activity was associated with the decrease of spike incidents.

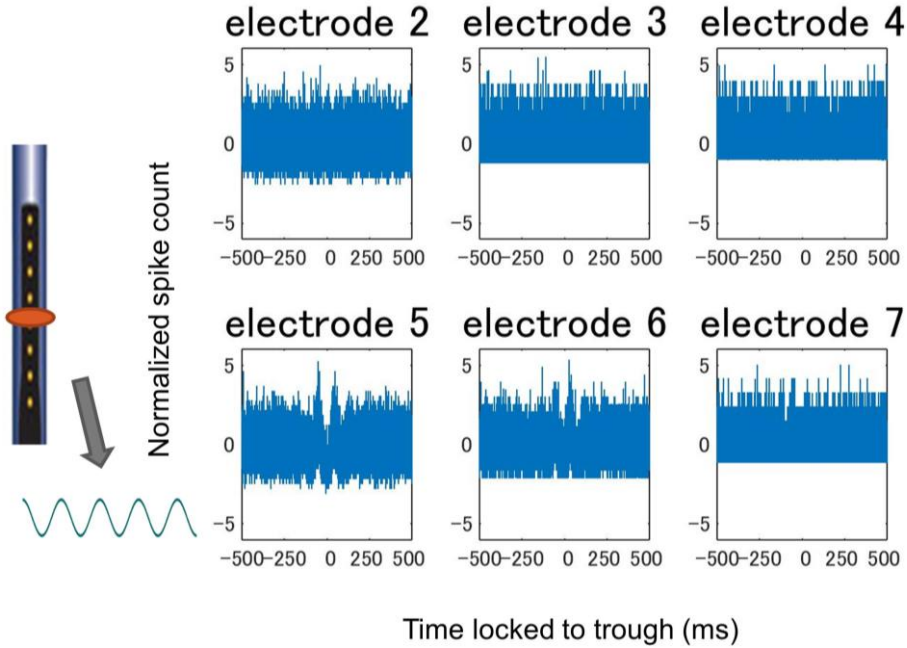


Figure 28. Plot of spike time-series in electrode 2, 3, 4, 5, 6, and 7. When locked to the trough of alpha activity in electrode 5, spiking activities in electrode 5 and 6 showed clear coupling. The phase trough was associated with the decrease of spike incidents.

Discussion

In the dorsolateral prefrontal cortex of one monkey, we found inter-layer phase-amplitude and phase-spike couplings. The existence of such couplings as computational mediums has revealed the intricacy of computation by oscillatory activities in the brain. Interestingly inter-layer alpha-gamma coupling showed distinctive characteristics. Aligning amplitude time-series to the phase activity of alpha oscillation in electrode 4, higher gamma-amplitude in electrode 4, 5, 6 and 7 were associated with the

alpha phase trough. Similarly, more spike incidents in electrode 5 and 6 were associated with the phase trough of electrode 4. Changing the locked electrode to electrode 5, the relationship between the phase trough and amplitude, and phase trough and spike became reversed. Namely, the phase trough was associated with lower gamma amplitude in electrode 4, 5, 6 and 7, and less spike incidents in electrode 5 and 6. Such complicated relationship might reflect the difference in signals coming from laminar layer 4 and 5. In a classical paper by Da Silva and Van Leeuwen (1977), they found opposite alpha phase in layer 4 and 5 in the visual cortex of dog. This suggests that the same inter-layer mechanism is replicated in the DLPFC. Furthermore, given we observed the alpha-gamma coupling in the DLPFC as reported in the primary visual cortex (Spaak et al., 2012), the coupling could be one of canonical computation the brain utilizes. Since the same laminar organization with minor variation is replicated across the entire cortex, they might rely on the same computational principles. (Bastos et al., 2012). This canonical computation would be a mechanism to organize spike train (Figure 27 and 28), and improve computational efficiency. The brain has to address different types of stimuli with distinctive temporal orders. If stimuli have temporal regularities, it would be natural for the brain to utilize it. Rather than being alert all the time, carrying out computation only when necessary would be more cost-effective. Phase-amplitude-spike coupling might be a mechanism to enable such efficiency.

General Conclusion

This dissertation has revealed brain's oscillatory process playing roles in information processing from local to global, internal to external and microscopic to macroscopic scales. In chapter 3, how local and global computations with distinctive characteristics were integrated was discussed. Specifically information exchanged globally through inter-regional synchrony became integrated with local computation via cross-frequency phase-amplitude coupling. In chapter 4, how oscillatory activity in the brain retrieved the characteristics of external stimuli and combined them with internal computation

were discussed. In the external world the brain has to interact with, diverse types of events such as speech are rhythmic. Exploiting such predictability would be parsimonious use of brain resources. Phase-synchrony between LFP and external stimuli could subserve the purpose by adjusting LFP phase with appropriate frequency to the corresponding phase of external stimuli. Temporal characteristics of external stimuli as they are might not fit to the temporal order of computation in the brain. CFC again could play a role to connect them. Finally, in chapter 5, physiological manifestation and function of CFC were explained. Having recorded signals from multiple layers, cross frequency coupling was revealed to support inter-layer communication. Additionally, the study observed inter-layer phase-spike coupling, which perhaps serves to modulate the probability of spike generation systematically such that efficient computation is possible. For future works, causality from one oscillation to another, and oscillation to spike is worthwhile to pursue. There has been a hypothesis arguing that lower-frequency LFP phase is a driving factor on higher-frequency LFP amplitude and spiking activities (Canolty et al., 2006; Giraud and Poeppel, 2012; van Atteveldt et al., 2014). Using statistical causal inference methods such as transfer entropy, information flow between one oscillation and another, and oscillation and spike can be tested (Kawasaki et al., 2014; Lobier et al., 2014). To summarize, the thesis has illustrated dynamics of LFP in information processing across multiple scales.

There have been renewed interests in LFP oscillation among neuroscience community for the recent decade, because of the development in novel recording technology and the advancement in understanding of how oscillation is involved in neural computation (Einevoll et al., 2012). However, experiments I have conducted and cited in this paper were mostly correlational. Needless to say, correlation is not causation. Some researchers remain skeptical about meaningful role of LFP oscillation in information processing of the brain, arguing that LFP oscillation is a by-product of spiking activities (Buzsáki 2009). The crucial question is whether LFP oscillatory activity is causal on information processing in the brain. To prove that, one needs some physical measures to manipulate oscillation alone

without affecting other processes. Transcranial alternate current stimulation (tACS) could induce electric current, which oscillates without causing neuronal depolarization (Zaghi et al., 2009). Using the technique, Polania et al. (2012) showed that entraining LFP oscillation across the frontoparietal network and inducing in-phase (0°) synchronization improved cognitive performance, whereas anti-phase (180°) synchronization deteriorated it. This result could be interpreted as tACS-induced change in LFP oscillation causally affecting inter-regional communication. Moreover, there have been a series of study which illustrated that brain rhythm has a causal relationship on spiking activities (Frohlich and McCormik, 2012; Anastassiou et al., 2011; Truccolo et al., 2009). These studies suggest that phase-spike coupling observed in chapter 5 was not correlational but LFP phase was a driving factor on spike train. In other words, LFP oscillation affects brain computation indirectly via spike activities at least. Furthermore, to think of LFP oscillation playing a role in the information processing of the brain would be more parsimonious explanation. Oscillations could naturally arise in the brain from opposite force such as ion influx and outflux or excitation and inhibition (Buzsáki 2009). This provides a way to coordinate computations across the regions in proper timing without having an additional mechanism for that. Therefore, from evolutionary perspective, it is reasonable to contemplate that the brain exploits this ‘free’ resource for efficient computation (Buzsáki 2009).

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Abbreviation

AHP: After hyper-polarization potential

CFC: Cross frequency coupling

CSD: Current source density

DLPFC: Dorsolateral prefrontal cortex

EEG: Electroencephalography

ERD: Event-related desynchronizations

ERP: Event-related potential

ERS: Event-related synchronization

LFP: Local field potential

PLF: Phase locking factor

PLV: Phase locking value

tACS: transcranial alternate current stimulation

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