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Cross-frequency coupling of brain oscillations: An impact of state anxiety

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ABSTRACT

In recent studies, statistical relations among activities in different frequency EEG bands have been reported. Most of these studies investigate within-subject cross-frequency relations, such as amplitude–amplitude, phase–amplitude and phase–phase coupling between different frequencies. All these cross-frequency interactions are considered to be transient correlates of information processing. However, some authors suggested that a particular pattern of amplitude–amplitude relations among different frequencies may be associated with relatively stable states or even traits. Particularly delta–beta amplitude–amplitude correlation measured in the between-subject domain was shown to lawfully increase in some presumably anxiogenic conditions and in some pathological groups. The main purpose of this paper was to further explore the phenomenon of between-subject delta–beta correlation in terms of its spatial localization, relatedness to state anxiety, and similarity to within-subject amplitude-to-amplitude and phase-to-amplitude coupling. Independent component analysis was used to identify temporally correlated spatial patterns that most reliably show the phenomenon of between-subject delta–beta correlation. Results of this analysis show that in an anxiogenic situation, delta–beta correlation increases in a network of cortical areas which includes the orbitofrontal and the anterior cingulate cortices as its main node. This increase of correlation is accompanied by an increase of delta power and connectivity in the same cortical regions. Analysis of the within-subject delta–beta amplitude-to-amplitude and phase-to-amplitude coupling showed that in an anxiogenic situation, in subjects with higher scores on state anxiety they also tend to increase in the same set of cortical areas.

1. Introduction

Frequency components of electroencephalogram (EEG) signal have become the main focus of interest for EEG researchers starting from the first observation by Berger (1929). The notion of possible functional relevance of these components underwent a thorough change in course of time from admitting that they are useful only for making inferences about global states of sleep and wakefulness (e.g. Duffy, 1962; Thayer, 1989) to acknowledging that oscillations may play a special role in large scale synchronization of brain functions (Buzsaki and Draguhn, 2004; Salinas and Sejnowski, 2001; Singer, 1999). Considerable evidence links different frequency brain oscillations with a range of cognitive processes, emotional states, and behaviors (Basar, 1999; Cantero and Atienza, 2005; Klimesch, 1999; Knyazev, 2007; Nunez, 2000; Varela et al., 2001). The functional significance of brain oscillations has usually been tested for the different frequency bands separately. Neuronal processing, however, involves simultaneous oscillations in various frequency bands (Basar, 2006), which raises the question about relationships between different oscillations.

In recent studies, statistical relations among activities in different frequency bands have been reported. These studies may be roughly divided into several categories. Firstly, a range of methods have been suggested to measure phase coordination between different frequencies, such as bicoherence (Schack et al., 2002), biphase-locking measure (Darvas et al., 2009), or "n:m" phase synchronization (Tass et al., 1998; Palva et al., 2005; Schack and Weiss, 2005). Cross-frequency phase coordination in the human brain suggests nonlinear interaction, and it is speculated that such interactions play a crucial role in the coordination of complex cortical computation (Darvas et al., 2009).

Amplitude–amplitude coupling is another type of cross-frequency relationship which has received relatively less attention. In the within-subject domain, amplitude–amplitude covariations among different frequencies have been considered as a form of neural coding (Friston, 1997). Bruns and Eckhorn (2004) observed a pronounced task-related increase of correlation between gamma-band (28–70 Hz) signal envelopes from a superior (occipital) and low-frequency (0–3.5 Hz) signals from an inferior (occipital) visual area, lasting for approximately 1 s and possibly reflecting a short-term memory encoding process. Thus, within-subject between areas amplitude–amplitude coupling can be indicative of two recorded areas belonging to the same functional group modulated by a common source (see Young and Eggermont, 2009 for a review).

Another type of cross-frequency coupling is called phase–amplitude coupling, and refers to a synchronization of oscillation power fluctuations with the phase of a slower oscillation (Jensen and Colgin, 2007). For example, in the entorhinal and prefrontal cortices, the amplitude of

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gamma oscillations increases during specific phases of theta (Chrobak and Buzsaki, 1998; Canolty et al., 2006; Demiralp et al., 2007), amplitude modulation of occipital high-frequency oscillations in the gamma range may be phase locked to a slow-frequency oscillation in the delta band (Handel and Haarmeier, 2009) and so on. Theta phase to gamma amplitude coupling have been extensively studied in the hippocampus of rodents and man where they are widely believed to reflect the integration of components to a single cognitive stream (Jensen and Lisman, 2005; Lisman, 2005; Lisman and Buzsaki, 2008). Studies in the monkey auditory cortex have revealed that this type of phase–amplitude coupling may be more widespread elsewhere in the brain (Lakatos et al., 2005). It was shown with multi-unit and field potential recordings that not only gamma power was modulated by theta phase, but in turn theta power was further modulated by ongoing delta phase. In addition, the multi-unit data show that spiking activity in the macaque auditory cortex is phase modulated by gamma, theta and delta phase.

All these cross-frequency interactions are considered to be transient correlates of information processing. However, some authors suggested that a particular pattern of amplitude–amplitude relations among different frequencies may be associated with relatively stable states or even traits. Thus, Robinson (2001) showed that the strength of negative association between amplitudes of filtered in alpha and delta frequency bands evoked potentials is lower in individuals with simultaneously high scores on both Extraversion and Neuroticism. Knyazev et al. (2003, 2004) repeated this analysis for recorded in resting state spontaneous EEG and obtained similar results. In both cases the alpha–delta anticorrelation was computed across subjects, i.e., in the between-subject domain. Knyazev and Slobodskaya (2003) found that the strength of analogous within-subject, i.e., across subject's states, alpha–delta anticorrelation is related to psychometric measures of Behavioral Inhibition. Knyazev (2007) summarized empirical evidence showing that amplitudes of alpha and low frequency oscillations (delta and theta ranges) tend to be reciprocally related to each other, with relative prevalence of low frequencies being associated with disinhibited behaviors.

Schutter and Van Honk (2004) were the first to discover that the magnitude of a (between-subject) correlation between delta and beta power in spontaneous EEG depends on the level of such hormones as cortisol and testosterone. Their studies provide strong evidence that the magnitude of across-subjects correlation between powers of slow (SW) and fast (FW) waves could be manipulated by factors that presumably change the subject's state. Particularly, this evidence appears to imply that the state of anxiety should be associated with increased correlation between delta and high frequency oscillations, because it was higher in subjects with higher baseline level of salivary cortisol (Schutter and van Honk, 2005), it increased after cortisol administration (van Peer et al., 2008), and it diminished after administration of testosterone (Schutter and van Honk, 2004), which inhibits the stress-induced activation of the HPA axis (Viau, 2002) and decreases sensitivity to punishment and anxiety (van Honk et al., 2004). Correspondingly, males who were high in baseline salivary testosterone exhibited significantly reduced prefrontal delta–beta correlation compared to those low in testosterone (Miskovic and Schmidt, 2009). Indeed, Knyazev et al. (2005, 2006) showed that, relative to baseline, the SW–FW correlation increased when subjects had to expect bad news but did not change when they expected good news. Moreover, this increase was more pronounced in subjects with a higher level of trait anxiety. Miskovic et al. (2010) showed that a high socially anxious group from normative population showed significantly greater SW–FW correlation than a low socially anxious group while anticipating a public speaking task.

A number of studies analyzed the SW–FW correlation in groups with anxiety-related pathological conditions. A study by Miskovic and Schmidt (2009) provides evidence that individuals diagnosed with social anxiety disorder (generalized subtype) exhibit high levels of EEG delta–beta correlation during the anticipation of a self-presentation task, whereas cognitive behavioral therapy significantly reduces the anticipatory delta–beta correlation. Moreover, higher frontal SW–FW correlation was registered in children of parents with social phobia, as compared to children of healthy parents (Miskovic et al., 2011). Somewhat discordant to these data, Velikova et al. (2010) have found lower SW–FW correlation in patients with obsessive–compulsive disorder than in age- and sex-matched controls. The authors suggest that obsessive–compulsive disorder is related not only to increased activation in frontal networks, but also to a frontal–subcortical functional disconnection.

These findings, particularly the findings of changed SW–FW correlation in pathological groups, are intriguing, but they leave a number of unresolved questions. Firstly, most published studies imply that state anxiety might be the psychological state underlying the emergence of the SW–FW coupling, but, to the best of our knowledge, a direct analysis of an association between individual differences in state anxiety and individual contribution to the emergence of the SW–FW coupling has never been done. Secondly, spatial localization of this effect is not consistently documented. In most of earlier studies, spectral power measures were averaged across electrode locations, thus precluding inferences about cortical localization of the effect. Some studies, however, show that this effect might primarily relate to prefrontal cortices (Schutter et al., 2006; Miskovic and Schmidt, 2009). It is clear, however, that, due to volume conduction, the EEG signal represents a mixture of signals coming from different sources. It has been claimed that some statistical methods, such as independent component analysis (ICA), may decompose data into maximally temporally independent components, representing the characteristic time and spatial signatures of the sources underlying the recorded mixed signal (McKeown et al., 1998). Later use of source modeling techniques may reveal possible cortical/subcortical localization of these sources. To the best of our knowledge, these approaches have never been used for analysis of the SW–FW correlation. Thirdly, in most relevant studies, the cross-frequency interactions are tentatively interpreted in terms of cortico-subcortical cross-talk. It should be borne in mind however that so far this interpretation is purely speculative. In all but one (Knyazev and Slobodskaya, 2003) studies, the cross-frequency correlation was measured in the between-subject domain, whereas the interpretation relates to the within-subject domain. Although Knyazev et al. (2004) found a good agreement between within- and between-subject measures of delta–alpha anticorrelation, such test, to the best of our knowledge, has never been done for the SW–FW coupling. Finally, the fact that the same frequencies are involved in the above discussed amplitude–amplitude SW–FW correlation and the well documented phase–amplitude SW–FW coupling may be not just a coincidence. The same mechanism may underlie both effects. Therefore simultaneous investigation of both effects on the same subjects and in the same conditions is necessary. Finally, when an association between two phenomena is observed, a lawful question would be about possible causal relationship. Analysis of causality is one of the emerging fields in EEG research. However, most of existing so far methods are inconclusive. Indirect evidence for inferring most probable direction of causality could be obtained from the analysis of temporal dynamics of each one of the two phenomena. For example, when in a certain situation and in certain subjects an increase (relative to baseline) of delta–beta coupling in certain cortical regions is observed, it would make sense to look how delta and beta power and connectivity in these same cortical regions changes in this situation and in these subjects. Event-related increase of power and connectivity in a frequency range may indicate the emergence of functional network whose activity is modulated by oscillations in this frequency range. Consequently, oscillations in this frequency range might be considered as the leading force which drives oscillations of the other frequency.

In the present study, we aimed (1) to directly evaluate an association between individual differences in state anxiety and individual contribution to the emergence of the delta–beta correlation in an anxiogenic situation; (2) to investigate cortical/subcortical localization