Electrophysiological correlates of cortico-subcortical interaction: A cross-frequency spectral EEG analysis

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Abstract

Objective: Several studies have provided evidence for the notion that the coupling between slow and fast frequency in the EEG spectrum indicates cortico-subcortical cross-talk (CSC-ct). In addition, findings for increased limbic activation due to reduced cortical inhibition have recently been acquired. To get further insights into these mechanisms, the current study investigated whether CSC-ct would decrease as a function of increased slow (SW) or fast wave (FW) activity.

Methods: Resting state EEG recordings were obtained from 46 healthy, right-handed participants. CSC-ct was quantified by computing cross-frequency correlations between the power in the slow and fast frequency range. CSC-ct was compared between groups with relatively low and high SW activity and groups with relatively low and high FW activity.

Results: Relatively reduced SW, but not FW activity was associated with a significant coupling between slow and fast frequency EEG. Furthermore, relatively enhanced resting state SW activity was paralleled by slow and fast frequency EEG decoupling.

Conclusions: These findings are in line with the notion that increased subcortical drive can go accompanied by reduced CSC-ct.

Significance: Cross-frequency EEG analyses might provide a unique approach to obtain novel insights into cortico-subcortical interactions in relation to affective and cognitive behavior.

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1. Introduction

Robinson's contribution in *Clinical Neurophysiology* (1999;110:1427–1434) on the technical, physiological, and psychological significance of frequency bandwidths in EEG evoked potentials hallmarked the onset of a new field of research, wherein different EEG rhythms in the cortical EEG reflect the different subcortico-thalamic-cortical projections. Robinson (1999) showed that the event-related brain potentials are comprised of frequency bandwidths that originate from different neural arousal systems in awake humans. Through recording the EEG responses to auditory tones and using narrow-band filters he was able to demonstrate the relatively distinct nature of the 4, 7 and 10 Hz component waves in the auditory evoked potentials. Neurological studies had already shown that stimulation of brain-stem ascending reticular activating system (ARAS) elicits 1–4 Hz (delta) cortical responses (Guyton, 1976), whereas stimulation of the limbic system evokes 7 Hz (theta) activity (Gray, 1982). In addition to demonstrating a relationship between 4 Hz activity and the ARAS, Robinson argued that the thalamus could have been responsible for producing the 10 Hz oscillations.

Comparative research has provided evidence for dominant EEG rhythms to shift with brain complexity. Whereas the reptile brain is suggested to be an arousal system oscillating in the delta range (Gaztelu et al., 1991), lower mammals have an additional limbic system that is

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associated with theta oscillations (Klimesch, 1999). Finally, primates are geared with a cortical mantle, which oscillates in the 8–12 Hz (alpha) and the 13–30 Hz (beta) frequency range (Knyazev and Slobodskaya, 2003). This is in line with Basar's (1998) notion on the evolutionary accounts of brain development stating that only the human EEG contains the entire delta to beta frequency spectrum. Thus, in addition to temporal EEG, analyses in the frequency domain might yield insights in physiological properties that can be linked to the different arousal systems and provide possible insights into how these systems communicate.

Moreover, studying the relations between the different frequency bandwidths could reveal some of the dynamics of these interacting systems. Knayzev et al. (2004), for instance, argued that the delta and alpha system operate in close conjunction during behavioral regulation. Evidence for this assumption was provided earlier by Robinson (1999), who observed a negative relationship between 4 Hz (i.e. delta-theta activity) and 10 Hz (i.e. alpha) activity that was attributed to thalamic inhibition of the brain-stem ascending reticular activating system (ARAS).

Interestingly, the negative relationship observed by Robinson fits John Hughlings Jackson's (1958) visionary principle of descending inhibition (DI), which states that the cortical system executes inhibitory control over lower brain structures. Exemplary in this context is a functional neuroimaging study, which showed that the voluntary control of negative feelings is associated with enhanced prefrontal cortex (PFC) activity and reduced amygdala activity (Ochsner et al., 2002). Moreover, Anderson et al. (2004) recently discovered that the involvement of prefrontal cortex in the active suppression of unwanted memories was accompanied by reduced hippocampal activation and impaired retention. On basis of the evidence above, DI might be considered an example of cortico-subcortical cross-talk (CSC-ct) as reflected in the coupling between frontal slow (SW) and fast wave (FW) activity. In agreement, Knyazev and Slobodskaya (2003) showed that the coupling between the slow and fast frequency range predicts behavioral inhibition. In concordance, Schutter and Van Honk (2005) found cortisol, a stress-hormone associated with behavioral inhibition and anxiety, to be linked to the coupling between SW and FW activity. Moreover, the administration of testosterone, a steroid associated with behavioral activation and fearlessness (Van Honk et al., 2004), induces increased SW activity and decoupling of SW and FW activity (Schutter and Van Honk, 2004). Notably, testosterone acts on steroid responsive networks in the limbic system (Hermans et al., 2004; Wood, 1996) and the findings by Schutter and Van Honk (2004) can therefore be explained in terms of subcortically driven reductions in CSC-ct resulting in behavioral activation. This also provides an alternative electrophysiological explanation for increased disadvantageous risky decision making in the Iowa gambling task after administrating testosterone to healthy volunteers (Van Honk et al., 2004). Successful performance in the Iowa gambling task depends on avoidance of initially rewarding, but eventually disadvantageous decks of cards (Bechara et al., 1994). In agreement, Schutter and Van Honk (2005) demonstrated that increased ratios between SW and FW activity predicted risky disadvantageous decision-making. Thus, relatively increased SW compared to FW activity might reflect reduced cognitive control that should be paralleled by increased subcortical motivational drive and reduced CSC-ct.

To seek further evidence for these presumptions, we investigated the role of SW and FW and their distinct contribution to CSC-ct on basis of the following hypotheses: If the subcortical system is controlling CSC-ct during relaxed wakefulness, subjects with relatively high SW activity will show SW–FW decoupling, whereas significant SW–FW coupling will be observed in subjects with relatively low SW activity. If, on the other hand, the cortical system is controlling CSC-ct, subjects with relatively high FW activity will display significant SW–FW coupling, while SW–FW decoupling will be observed for subjects with relatively low FW activity.

2. Methods

2.1. Subjects

Forty-six healthy right-handed volunteers (35 females) aged between 18 and 24 years were recruited at Utrecht University, The Netherlands. All participants were medication free, except for the females taking oral contraceptives, had at least 12 years of education and written informed consent was obtained. All volunteers were unaware of the aim of the study and were paid for participation. The study was approved by the local ethical committee of the Faculty of Social Sciences.

2.2. Resting state EEG recording

EEG was recorded from 32 scalp locations according to the International 10–20 EEG System using Ag-AgCl-tipped electrodes (sampling rate: 256 Hz). Electro-oculogram (EOG) was recorded from a bipolar montages from the sub- and supra-orbital regions of the right eye and the outer canthi of the eyes. Raw EEG recordings were made with the ActiveTwo system (BioSemi, Amsterdam, The Netherlands) relative to the common mode sense (CMS). By physically integrating the first amplifier stage with a sintered Ag–AgCl electrode, extremely low-noise recordings free of interference can be achieved. The Active-electrode is a sensor with very low output impedance. The ground consisted of the active CMS active and passive driven right leg (DRL) electrode that form a feedback loop driving the subject's average potential as close as possible to the analog-to-digital converter (i.e. the amplifier 'zero')

reference voltage in the A/D-box. In sum, the ActiveTwo system does not require impedance measurements or gain adjustments (www.biosemi.com).

2.3. Procedure

Upon arrival at the laboratory, participants were screened for the presence of neurological or psychiatric conditions. Drug use other than oral contraceptives was considered as an exclusion criterion. The consumption of maximal fourteen alcoholic beverages per week was allowed and all subjects were non-smokers. The EEG recording procedure was explained to the subjects and informed consent was obtained. Subjects were seated in a comfortable dentist chair in a dimly lit room adjacent to the control room and instructed to relax and keep movements to an absolute minimum. A 4 min resting state EEG, in which 1 min of eyes open was alternated by 1 min of eyes closed was recorded. Afterwards subjects were debriefed and received their participation fee.

2.4. Data reduction and analysis

Raw EEG signals were referenced to the average signal of the 32 electrodes, chunked into 4 s epochs and corrected for horizontal and vertical eye movements using the Gratton & Coles method (BrainVision, Munich). EEG epochs containing residual muscle movements and other artifacts resulting in amplitudes greater than $+/-50\,\mu V$ were rejected prior to further analysis. The designation of an artifact in one of the leads resulted in removal of that epoch for all channels in order to ensure that the remaining data were identical for all sites in time. Chunks of averaged artifact-free EEG were filtered by applying a band-pass of 1–30 Hz (24 dB/octave) and a fast Fourier transform method (Hamming window length: 10%) was applied to obtain estimates of spectral power (μV^2) in the delta (1–3 Hz), theta (4–7 Hz) and beta (13–30 Hz) frequency band for the mid-frontal (Fz) electrode site (for the rationale see Michel et al., 1992; Schutter and Van Honk, 2004, 2005). Low and high SW (i.e. delta and theta activity) groups and low and high FW (i.e. beta activity) groups were created through a median split to allow 6 planned group comparisons of the Pearson's correlations between delta–beta and theta–beta power. A Steiger test was performed to test for significant differences between the correlations (Clark-Carter, 1997). The alpha level of significance was set at 0.05 throughout.

3. Results

As can be seen from Fig. 1, the expected coupling between SW delta and FW beta activity was observed in the low [$r(23)=0.62$: $P=0.002$], whereas decoupling between delta and beta activity was observed in the high resting state delta activity group [$r(23)=0.02$: $P=0.93$]. The group difference in correlations was statistically significant [$Z=2.20$: $P=0.01$].

Similar coupling and decoupling was observed for the low [$r(23)=0.63$: $P=0.001$] and high resting state theta activity group [$r(23)=-0.02$: $P=0.93$]. The group difference in correlations was also statistically significant [$Z=2.25$: $P=0.01$]. Fig. 2 displays the coupling and
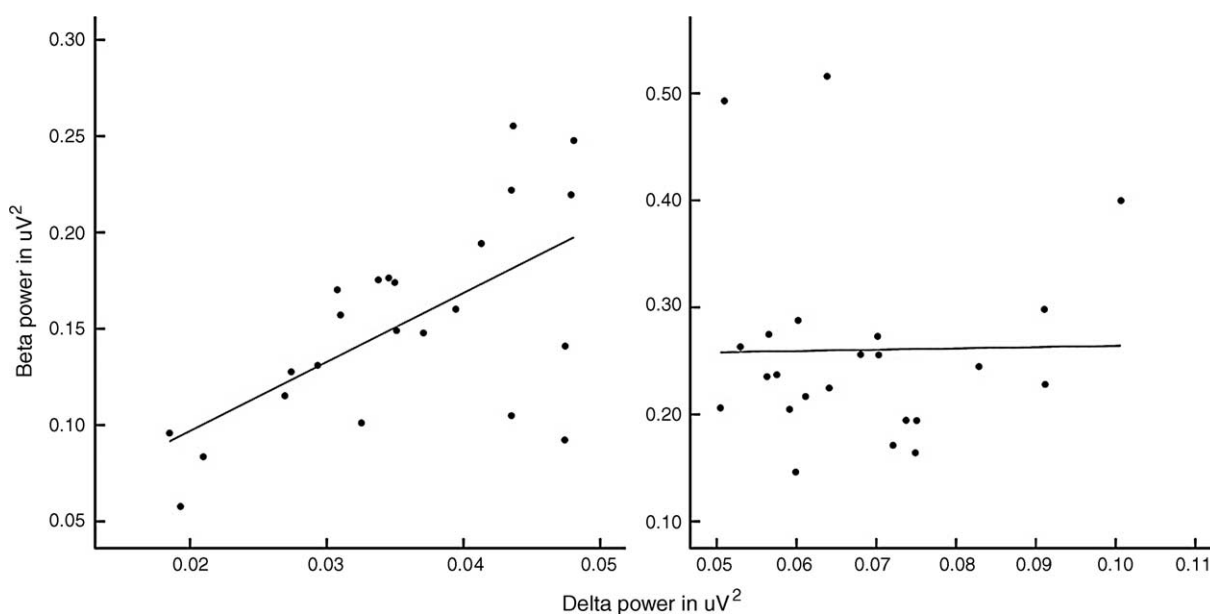

Fig. 1. Scatterplots of significant delta–beta correlation in the low resting state delta activity group (left panel) that is absent in the high resting state delta activity group (right panel).
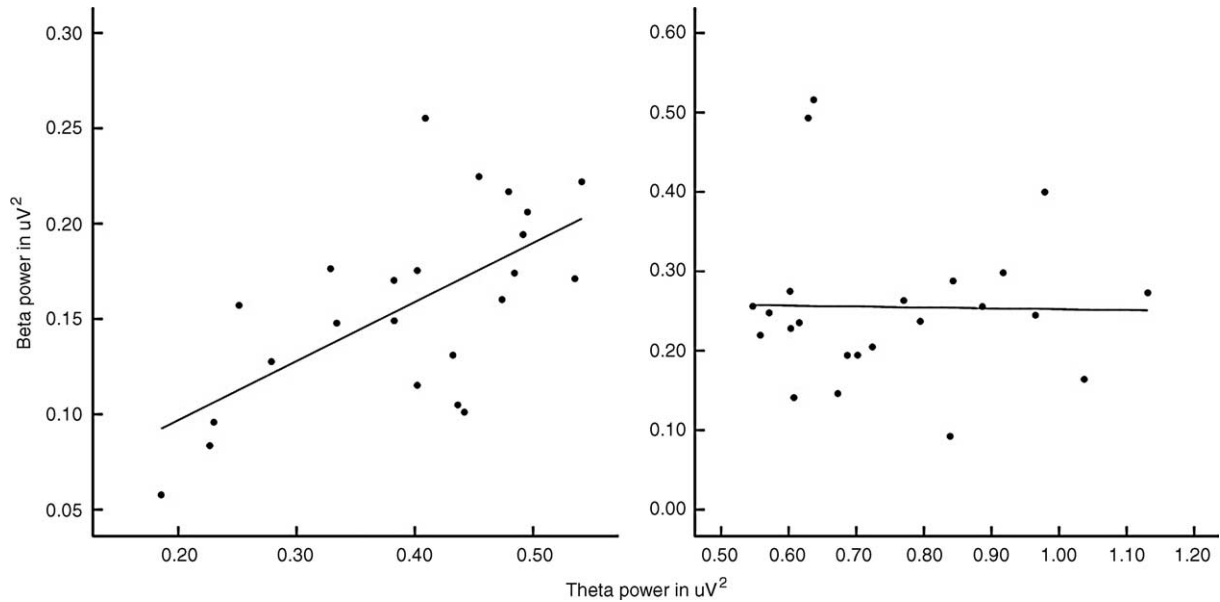
Fig. 2. Scatterplots of significant theta–beta correlation in the low resting state theta activity group (left panel) that is absent in the high resting state theta activity group (right panel).

decoupling for the low and high resting state theta activity group, respectively.

No significant differences in delta-beta coupling [$Z = 1.3$: $P = 0.1$] were observed between the low [$r(23) = 0.51$: $P = 0.01$] and high FW activity group [$r(23) = 0.15$: $P = 0.50$]. The scatterplots are depicted in Figs. 3 and 4. The lack of difference in theta-beta coupling [$Z = 0.40$: $P = 0.34$] was also seen between the low [$r(23) = 0.31$: $P = 0.15$] and high FW activity group [$r(23) = 0.19$: $P = 0.39$]. These findings suggest that during relaxed

wakefulness cortical CSC-ct supervenes on the subcortical rather then the cortical system.

4. Discussion

The present study investigated whether SW or FW activity would predict CSC-ct during relaxed wakefulness. Results showed that relatively high versus low SW, but not high versus low FW activity during resting state was
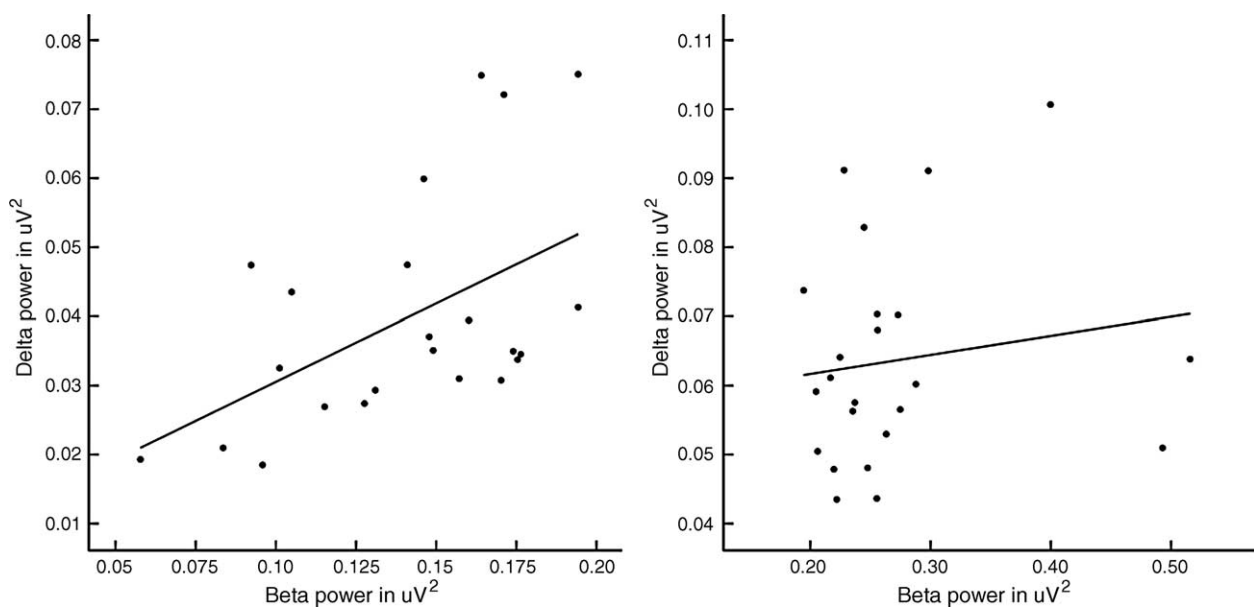

Fig. 3. Scatterplots of non-significant difference between delta–beta correlation in the low resting state beta activity group (left panel) and the high resting state beta activity group (right panel).
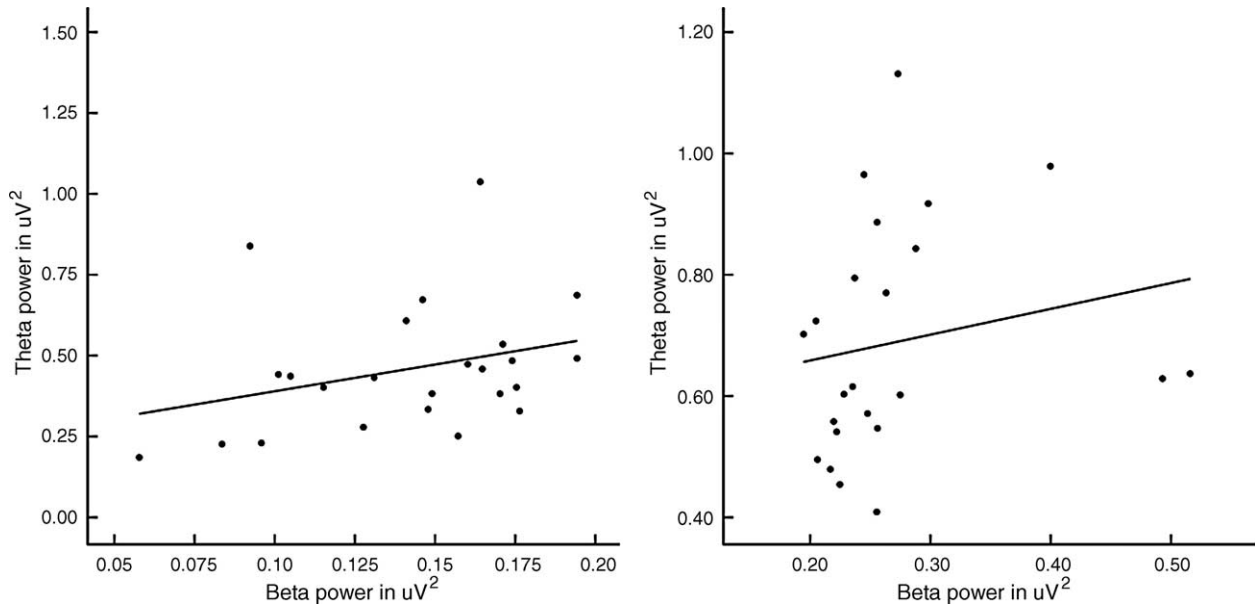
Fig. 4. Scatterplots of non-significant difference between theta-beta correlation in the low resting state beta activity group (left panel) and the high resting state beta activity group (right panel).

accompanied by the decoupling of slow and fast frequency EEG. These data indicate that, at least during resting state conditions, CSC-ct is predominantly controlled by the subcortical system.

Several lines of evidence suggest that the frequency-related information of the EEG can be linked to functionally distinct neuronal systems (Robinson, 1999). Delta activity is assumed to reflect general arousal and motivation-related processing that presumably originates from subcortical (limbic) brain structures. This is supported by studies showing relationships between delta activity and approach-related behavioral indices, including reward sensitivity, aggression and sex drive (Knyazev et al., 2004; Scarpa and Raine, 1997). As already noted in the introduction, Schutter and Van Honk (2004) showed that the administration of testosterone in healthy volunteers elevates delta activity, which can likewise be explained in terms of increased reward-related motivational drive.

Furthermore, Van Honk et al. (2004) demonstrated that the approach-related motivational properties of testosterone involve a shift towards increased reward and reduced punishment sensitivity. Although the sensitivity for punishment as manifested by significant CSC-ct should normally guide behavior towards advantageous non-risky choices, testosterone arguably excites the subcortical arousal and reward systems, consequently shutting down the regulatory function of the cortex. In concordance, a brain SPECT study by Amen et al. (1996) showed that decreased PFC activity in conjunction with increased limbic activity relates to approach-related aggressive behavior. Furthermore, Loo et al. (2004) demonstrated that methylphenidate responses in ADHD not only include increased frontal beta EEG activity, but also enhanced response inhibition and reduced impulsivity. These findings concur with the presently advocated view of a dual-systems model of cortical top-down emotion regulation. Thus, whereas behavioral activation is arguably related to increased subcortical drive in combination with reduced cortical coupling (Schutter and Van Honk, 2004), behavioral inhibition and anxiety should be linked to lowered subcortical drive as a consequence of enhanced DI (Knyazev et al., 2004). In addition, Knyazev et al. (2003, 2005) have argued that subjects with relative high baseline delta power and SW–FW decoupling might be in a more relaxed non-anxious state, whereas relative low baseline delta power and SW–FW coupling should reflect increased anxiety. This explanation fits the notion of increases in the behavioral activation system (BAS) (Knyazev et al., 2003, 2005) and concurs with evidence of increased delta-beta coupling during anticipatory anxiety (Knayzev et al., unpublished data).

While the BAS has been linked to left-sided dominance in cortical lateralization models (Harmon-Jones, 2003), there are data suggesting a link between the BAS and the lower subcortical level also. Putman et al. (2004) showed that BAS was associated with emotional responses to angry faces in a masked task that is insusceptible to voluntary control (for details, see Van Honk et al., 1998; Van Honk et al., 2000). Masked emotional stimuli tap into the lower subcortical structures circumventing the higher cortical regulatory system (LeDoux, 1996; Van Honk et al., 2005). The responses to the masked angry faces observed by Putman et al. (2004) hypothetically reflect subcortically generated behavioral activation deprived of cortical coupling.

In short, although there is evidence from EEG and transcranial magnetic stimulation studies for cortical

involvement in consciously accessible aspects of motivation and emotion (Harmon-Jones, 2003; Schutter et al., 2001), differences in motivational drive in terms of behavioral inhibition and behavioral activation seem also measurable as variability in CSC-ct across individuals. Reduced SW activity in healthy awake subjects has been associated with increases in both behavioural inhibition and CSC-ct, whereas heightened SW activity is linked to increased behavioural activation and reduced CSC-ct. Together with the observation that FW activity does not significantly modulate CSC-ct, the findings illustrate that humans are in essence emotionally and not cognitively driven operating systems during relaxed wakefulness (Panksepp, 2003).

Although the spatial resolution of EEG is limited, dipole source localization of resting state EEG in-awake healthy subjects (Michel et al., 1992) has provided some evidence for the notion that SW activity has a deeper neuronal origin (Hjorth and Rodin, 1988). SW and FW activity can be linked to the motivational and cognitive system, but at present there is no direct empirical evidence confirming the relationship between the particular frequency bandwidths and the distinct neuronal arousal systems. Nevertheless, taken together with the findings of Robinson (1999) the evidence presently provided suggests that cross-frequency relationships in the EEG can be used to investigate physiological brain properties such as the functional interaction between the affective and the cognitive system.

In sum, EEG technology will unlikely be capable of solving the localization issue, and the specific functional interpretation of delta and theta activity in relation to beta activity warrants further research. However, there is accumulating evidence that the link between the slower and faster frequency bandwidths provides an electrophysiological working model for investigating cortico-subcortical interactions.

In conclusion, cross-frequency analyses can reveal physiological dynamics of brain function that are unattainable in functional neuroimaging research. Therefore, the study of the relationship between slow and fast wave EEG activity may endow researchers with a framework that can broaden the understanding of the neurophysiological mechanisms linking affect and cognition.

Acknowledgements

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