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ORIGINAL ARTICLE

Estimation of testosterone/cortisol ratio by resting state EEG delta/beta ratio in elderly people

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Abstract

OBJECTIVES: Testosterone and cortisol are the end products of the hypothalamus-pituitary-gonadal and hypothalamus-pituitary-adrenal axes. Both hormones affect brain anatomy and brain activity, which is positively correlated with the testosterone/cortisol ratio. The aim of the present study was to observe the main effect and interaction between testosterone and cortisol in relation to brain activity and whether it is possible to predict neuroendocrine levels.
METHODS: Sixty-seven participants were included for evaluating saliva hormones and resting state EEG. The levels of cortisol and testosterone were measured by enzyme-linked immunosorbent assay. The free artifacts of the EEG signals was computed and compared with the normative database.
RESULTS: The results showed that the testosterone/cortisol ratio was 34.21±3.75 in males, 19.92±1.47 in females and 24.19±1.71 among all participants. The testosterone/cortisol ratio and the resting state EEG delta/beta ratio were correlated at the frontal area, the central area, the parietal area and the left temporal area but not at the right temporal area or the occipital area. The resting state EEG delta/beta ratios of the frontal and central areas were used in a multiple regression model to predict the testosterone/cortisol ratio as 32.0% in males, 11.9% in females and 14.3% among all participants.
CONCLUSION: Resting state EEG is a non-invasive approach that can be used to estimate hormone levels, which are possible biomarkers of physiological and psychological disorders.

INTRODUCTION

The world's aging population is rapidly increasing in most developing countries from an estimated 901 million people aged 60 years or over in 2015 to an estimated 1.4 billion by 2030 and to nearly 2.1 billion by 2050 (United Nations 2015). With increasing life spans of elderly there are also increases in age-related disease such as dementia, cardiovascular disease (CVD), diabetes, mental health disorders and cancer. Most age-related diseases are endocrine disorders such as hypothalamus-pituitary-gonadal (HPG) axis and hypothalamus-pituitary-adrenal (HPA) axis disorders. The HPG axis controls development, reproduction and aging. Gonadotropin-releasing hormone (GnRH)

is produced in the hypothalamus by GnRH-expressing neurons. GnRH is released into the hypophyseal portal system and binds to secretory cells of the anterior pituitary (adenohypophysis). These cells produce luteinizing hormone (LH) and follicle-stimulating hormone (FSH), which are transported to the gonads, producing estrogen in females and testosterone in males (Sivan & Craig 2005; Michael 2006). The HPA axis controls the immune system, reproduction and emotion regulation. Corticotrophin releasing hormone (CRH) and arginine vasopressin (APV) are released from the hypothalamus and initiate adrenocorticotropic hormone (ACTH) production and secretion from the pituitary gland. CRH also activates the adrenal gland where glucocorticoids are produced (Elizabeth *et al.* 1992; Sean & Wylie 2006; Robert & Michael 2014). The end products of the HPG and HPA axes are testosterone and cortisol, respectively. HPA function is inhibited by testosterone at the hypothalamic level by decreasing arginine vasopressin (AVP) function, whereas HPG function is inhibited by cortisol at the hypothalamic, pituitary and gonad levels (Victor 2002). Moreover, testosterone and cortisol bind to the steroid-responsive center in the amygdala (Ruth 1996). Chronic high cortisol causes functional atrophy of the HPA axis, the hippocampus, the amygdala and the frontal lobe in the brain (Monica *et al.* 1992; Sonia *et al.* 1998; Bruce *et al.* 2016). The hippocampus is the brain region related to dementia, including Mind cognitive impairment (MCI) and Alzheimer's disease. Basal cortisol elevation causes damage to the hippocampus, leading to hippocampal atrophy and impairing hippocampus-dependent learning and memory (John *et al.* 2006; Vivian *et al.* 2013; Julius *et al.* 2015). The hippocampus has also been reported in stress and anxiety depression (Elizabeth *et al.* 1992; Constantine & George 2002; Dick *et al.* 2005; Dirk *et al.* 2009). Conversely, testosterone increases neural activity in the amygdala and influences orbitofrontal cortex activity (Birgit *et al.* 2009; Guido *et al.* 2009). Testosterone influences mood regulation, decision-making and sexual function. Low testosterone is associated with depression and impaired spatial cognition (Michael 2006). Thus, imbalance of the HPA and HPG axes is associated with psychopathy (Andrea *et al.* 2011). The cortisol/testosterone ratio may predict approach motivation or reward sensitivity and aggressive behavior (David *et al.* 2009). Moreover, the cortisol/testosterone ratio is significantly correlated with homocysteine levels in acute myocardial infarction patients, and this biomarker may indicate increased risk of CVD (Shahid *et al.* 2010).

Both hormones affect brain activity. Testosterone administration was reported in the decoupling of subcortical (delta) and cortical (beta) activity at midfrontal electrode sites (Dennis & Jack 2004), whereas cortisol administration was reported in the coupling of subcortical (delta) and cortical (beta) at midfrontal electrode sites (Dennis & Jack 2005; Jacobien *et al.* 2008). Furthermore, relative increases in the alpha band at the right frontal region significantly altered frontal asymmetry and reduced approach motivation (Mattie *et al.* 2005; Mattie *et al.* 2006; Mohammad *et al.* 2017). Acute stress decreased the theta and alpha bands with increasing cortisol levels (Bryan *et al.* 2017) and suppressed perception learning (Hubert *et al.* 2017). Moreover, brain activity in the amygdala, the hypothalamus and the brainstem was positively correlated with the testosterone/cortisol ratio (Erno *et al.* 2008). Thus, electroencephalography measurements may predict hormone levels.

The electrical activity of neurons is affected by both hormones, and thus, it is possible to predict neuroendocrine levels based on electroencephalogram (EEG) as a new biomarker. This study aimed to observe the main effect and interaction between testosterone and cortisol hormone levels in relation to brain activity as a non-invasive biomarker of neuroendocrine function for assessing physiological and psychological disorders in elderly people.

MATERIAL AND METHODS

Participants

One hundred ninety-three participants were recruited from the Brain Healthy Project of Mahidol University. Participants were excluded from this study if they were under 50 years of age or had a history of epilepsy or migraines, resting heart rate > 120 beats per minute, resting systolic blood pressure > 180 mmHg, resting diastolic blood pressure > 100 mmHg or SpO2 < 90 %. Sixty-seven participants were finally included (male=20 and female=47), and all provided written informed consent prior to participation.

Procedure

In the morning between 0800 h and 1100 h, all participants rinsed their mouth with water and spit into a saliva container to collect approximately 5 mL of saliva. The saliva samples were collected in approximately 15-minute intervals and kept at 4 °C. The levels of cortisol (nmol/L) and testosterone (pmol/L) in the samples were measured by enzyme-linked immunosorbent assay (ELISA) at iPath Medlabs Pty Ltd., Australia. Brain activity was recorded using a BrainMaster Discovery 24E system. Signals were recorded by 24-bit analog-to-digital converters at a 256-Hz sampling rate and DC bandwidth of 0.00 Hz to 80.00 Hz for 5 minutes in eyes-open condition. The recording EEG electrodes were placed according to the International 10-20 system for EEG at Fp1, Fp2, F3, F4, F7, F8, Fz, C3, C4, Cz, T3, T4, T5, T6, P3, P4, Pz, O1, and O2 locations with a referential montage (Marc *et al.* 1998). The free artifacts of 1 minute of EEG from the 5 minutes had a test re-test reliability >0.90 and a split-half reliability >0.95. The absolute power of these free artifacts of the EEG signals was computed and compared with the NeuroGuide normative database (Z score FFT absolute power, 625

individuals, 2 months – 82.6 years). The bands of the brain activity included delta 0.5–4 Hz, theta 4–8 Hz, alpha 8–12 Hz and beta 12–25 Hz. This study was approved by the Medical Ethical Committee of Mahidol University with certificate of approval (COA) number MU-IRB 2013/042.1004.

Statistics

The statistical analyses were performed using IBM SPSS Software Ver 18.0 for Window 8. The data were tested for normality using the Shapiro-Wilk test, and the means were calculated. The means of the results were compared between males and females using Mann-Whitney U tests for non-normal datasets and T-tests for normal datasets with 95% confidence intervals. The correlation between salivary hormones and brain activity was analyzed by Pearson correlation with 95% confidence intervals and multiple regression analysis was then used to predict the testosterone/cortisol ratio.

RESULTS

Dempgraphic characteristics

The study population included 67 participants (20 males and 47 females). The average age was 68.28 years (SD=6.99) across all participants, 68.95 years (SD=6.28) in males and 68.00 years (SD=7.32) in females. An independent-sample t-test indicated that age was not significantly different between genders (t(65)=0.506, p=0.651, d=0.14).

Saliva hormone

The average of testosterone levels were 177.90 pmol/L (SD=12.92) among all participants, 274.95 pmol/L (SD=25.87) in males and 136.60 pmol/L (SD=9.99) for females. The cortisol levels were 8.43 mmol/L (SD=0.55) among all participants, 9.22 mmol/L (SD=0.98) in males and 8.09 mmol/L (SD=0.66) in females. The average of testosterone/cortisol ratio was 24.19 (SD=1.71) among all participants, 34.21 (SD=3.75) in males and 19.92 (SD=1.47) in females. The saliva hormone was non-normally distributed. The Mann-Whitney U test indicated that the testosterone level (U=123.5, p=0.000, r=0.58) and testosterone/cortisol ratio (U=229.0, p=0.001, r=0.40) were significantly different but the cortisol level (U=384.5, p=0.241, r=0.14) was not significantly different between genders (Figure 1).

Brain activity

The average of resting state EEG delta/beta ratio was calculated for six brain areas based on electrode locations of the International 10-20 system for EEG electrode placement. The EEG delta/beta ratio was –0.38 (SE=0.11) for the frontal region (Fp1, Fp2, F7, F3, Fz, F4, F8) among all participants, –0.20 (SE=0.23) in males, and –0.46 (SE=0.12) in females; –0.72 (SE=0.11) for the central region (C3, Cz, C4) among all participants, –0.38 (SE=0.24) in males and –0.86 (SE=0.11) in females; –0.12 (SE=0.10) for the left temporal region (T3, T5) among all participants, –0.04 (SE=0.22) in males and –0.16 (SE=0.11) in females; –0.70 (SE=0.11) for the parietal region (P3, Pz, P4) among all participants, –0.44 (SE=0.23) in males and –0.81 (SE=0.12) in females; –0.25 (SE=0.12) for the right temporal region (T4, T6) among all participants, –0.24 (SE=0.23) in males and –0.25 (SE=0.14) in females; and –0.20 (SE=0.13) for the occipital region (O1, O2) among all participants, 0.05 (SE=0.27) in males and –0.31 (SE=0.15) in females. An independent-sample t-test indicated that the resting state EEG delta/beta ratio at the central area (t(65)=2.00, p=0.049, d=0.50) was significantly different between genders but the resting state EEG delta/beta ratio at the frontal area (t(65)=1.076, p=0.286, d=0.28), the right temporal area (t(65)=0.045, p=0.964, d=0.01), the left temporal area (t(65)=0.579, p=0.564, d=0.14), the parietal area (t(65)=1.561, p=0.123, d=0.40) and the occipital area (t(65)=1.271, p=0.208, d=0.33) were not significantly different between genders (Figure 2).

Correlation of saliva hormone and brain activity

The testosterone level was positively correlated with cortisol level (Pearson's r(67)=0.273, p=0.026) and the testosterone/cortisol ratio (Pearson's r(67)=0.704,

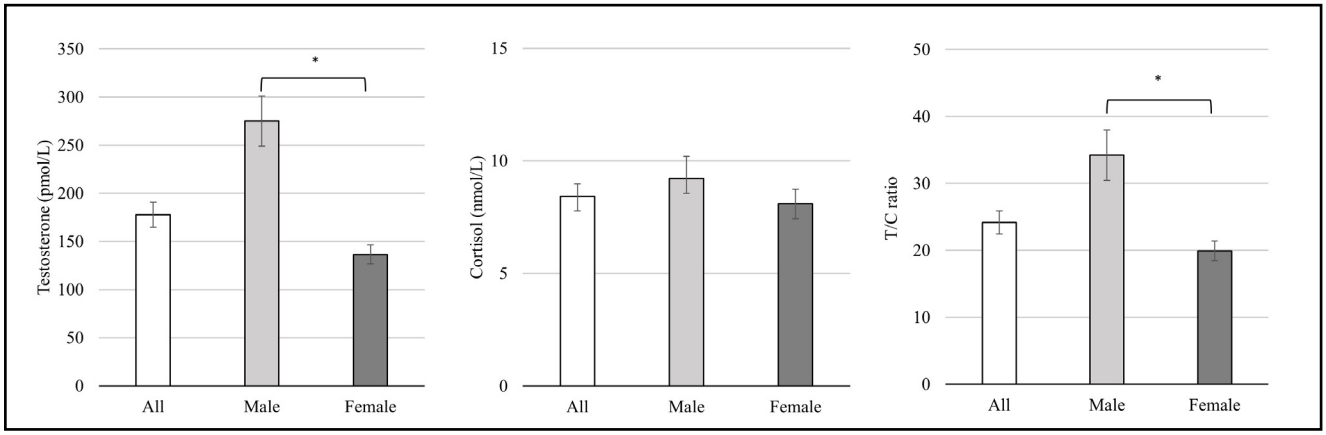

Fig. 1. The average testosterone levels, cortisol levels and T/C ratios (*p<0.05).

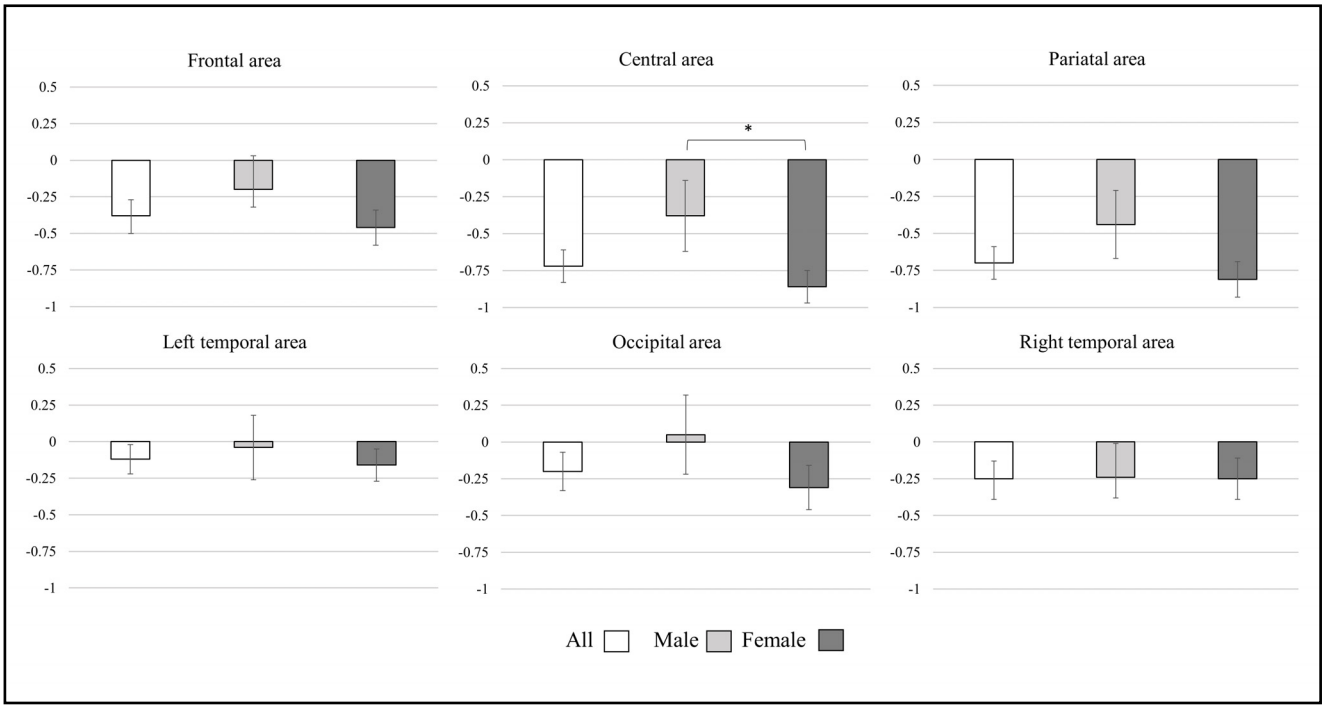

Fig. 2. The average of resting state EEG delta/beta ratio among brain areas (*p<0.05).

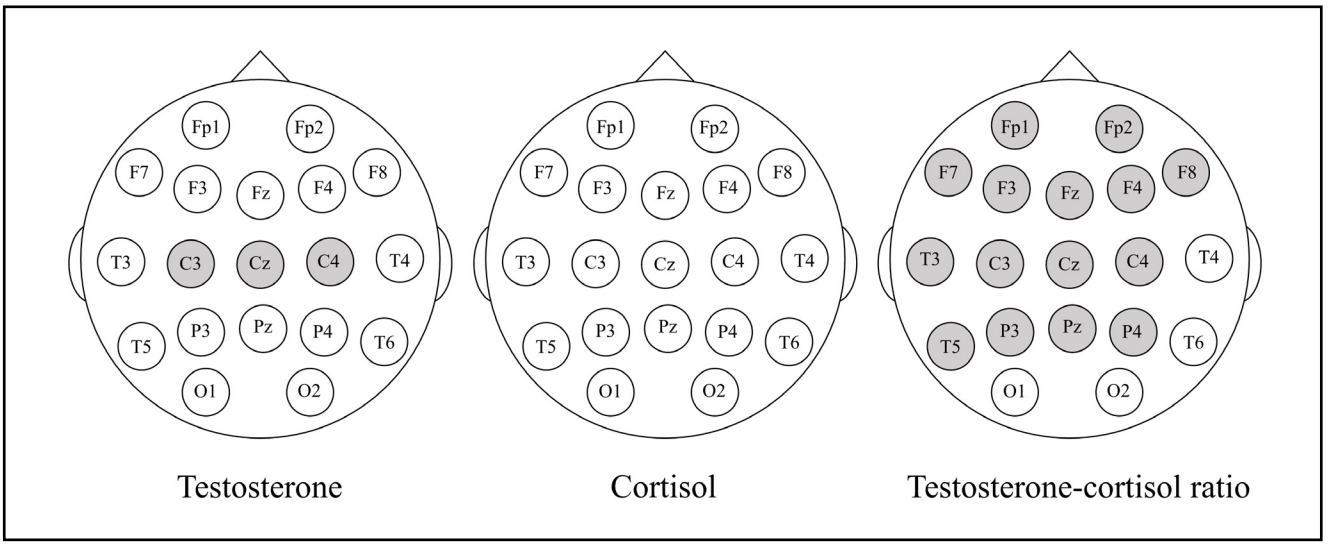

Fig. 3. The gray circles indicate brain regions with Pearson correlation between saliva hormones and the resting state EEG delta/beta ratio.

p=0.000). Moreover, the testosterone level was correlated at the central area (Pearson's r(67)=0.276, p=0.024). Pearson correlation analysis revealed that the testosterone/cortisol ratio and the delta-beta ratio were correlated at the frontal area (Pearson's r(67)=0.257, p=0.036), the central area (Pearson's r(67)=0.395, p=0.001), the parietal area (Pearson's r(67)=0.282, p=0.021) and the left temporal area (Pearson's r(67)=0.241, p=0.049) but not at the right temporal area (Pearson's r(67)=0.141, p=0.254) or the occipital area (Pearson's r(67)=0.208, p=0.098). In contrast, cortisol level was not correlated with brain activity (Table 1 and Figure 3).

Estimation of saliva hormone by brain activity

Multiple regression analysis was then used to predict the testosterone/cortisol ratio. Based on the analysis, the delta-beta ratios at the frontal and central areas were included in the multiple regression model. The results of the regression indicated that the predictor (the resting state EEG delta/beta ratio) at the frontal area (β=9.821, p=0.006) significantly predicted the testosterone/cortisol ratio in males, explaining 35.5% of the variance (R^2=0.355, F(1,18)=9.924, p=0.006); that the resting state EEG delta/beta ratio at the frontal area (β=–5.252, p=0.024) and central area (β=6.776,

Tab. 1. Correlations between saliva hormones and brain activity.

	1	2	3	4	5	6	7	8	9
1. Testosterone	–	0.273*	0.707*	0.204	0.276*	0.109	0.233	0.097	0.227
2. Cortisol		–	–0.423*	–0.078	–0.144	–0.196	–0.078	–0.096	0.027
3. T/C ratio			–	0.257*	0.395*	0.241*	0.282*	0.141	0.204
4. Frontal area				–	0.679*	0.529*	0.526*	0.414*	0.500*
5. Central area					–	0.692*	0.849*	0.478*	0.689*
6. Left temporal area						–	0.686*	0.726*	0.627*
7. Parietal area							–	0.522*	0.843*
8. Right temporal area								–	0.531*
9. Occipital area									–

Note. T/C ratio = testosterone/cortisol ratio, *p-value of Pearson correlation test <0.05

p=0.007) significantly predicted the testosterone/cortisol ratio in females, accounting for 15.7% of the variance (R^2=0.157, F(2,44)=4.112, p=0.023); and that the delta/beta ratio at the central area (β=6.079, p=0.001) significantly predicted the testosterone-cortisol ratio among all participants, accounting for 15.6% of the variance (R^2=0.156, F(1,65)=11.990, p=0.001).

DISCUSSION

The aim of this study was to observe the main effect and interaction between testosterone and cortisol hormone levels in relation to brain activity. In the biological mechanism interconnecting both hormones, cortisol is the end-product of the HPA axis. The hypothalamus and pituitary are parts of the pathway of the HPA and HPG axis. Cortisol inhibits all levels of the HPG axis, while testosterone inhibits the HPA axis at the hypothalamic level by decreasing AVP function. Our findings revealed that the testosterone level in males was higher than in females and associated with significantly increased resting state EEG delta/beta ratio in the midbrain region (C3, Cz, C4). This result showed that cortical activity was deactivated while subcortical activity was activated by testosterone and associated with rapidly reduced functional coupling of the amygdala with the orbitofrontal cortex and enhanced amygdala coupling with the thalamus. This finding supports previous studies that testosterone administration led to decoupling of sub-cortical (delta) and cortical (beta) activity at midfrontal electrode sites (Dennis & Jack 2004). Additionally, dominant aggressive behavior in both males and females has been associated with high testosterone, whereas cortisol levels do not differ between genders (Charlotte *et al.* 2009) and are not correlated with the resting state EEG delta/beta ratio. However, cortisol enhances the functional connectivity of subcortical and cortical regions. Cortisol administration was shown to significantly enhance mid-frontal delta-beta coupling and to modulate EEG alpha asymmetry. Similar patterns of activity have been reported in depression (Mattie *et al.* 2005; Dennis & Jack 2005; Jacobien *et al.* 2008). The interconnection of both hormones, the hypothalamus and the pituitary all contribute to the HPA and HPG axis. The testosterone/cortisol ratio was positively correlated with brain activity in the amygdala, the hypothalamus and the brainstem (Erno *et al.* 2008). The delta wave reflects the activity of subcortical networks, including the brainstem and the septo-hippocampal complex, while higher frequencies reflect the thalamo-cortical and cortico-cortical circuits (Gennadij & Helena 2003; Dennis & Jack 2005; Knyazev 2007; Dennis & Gennady 2012). Delta and beta oscillation has been used as an index of sub-cortical – cortical interactions. Testosterone and cortisol affect both subcortical and cortical areas (Dennis *et al.* 2006).

Additionally, this study aimed to predict neuroendocrine levels by variables of electrical brain activity. The results show that the ratio of testosterone to cortisol was significantly correlated with the resting state EEG delta/beta ratio at the frontal area (Fp1, Fp2, F7, F3, Fz, F4, F8), the central area (C3, Cz, C4), the left temporal area (T3, T5) and the parietal area (P3, Pz, P4). Thus, the resting state EEG delta/beta ratio can be used as an index to non-invasively estimate hormone levels. Variables for estimating the testosterone/cortisol ratio may include gender and the resting state EEG delta/beta ratios at the frontal, central, left temporal and parietal areas. However, the resting state EEG delta/beta ratio at the frontal and central areas was used in a multiple regression model to predict testosterone/cortisol ratios of 32.0% in males, 11.9% in females and 14.3% among all participants (Figure 4.).

Notably, testosterone levels in males were higher than in females. Testosterone was a strong variable in the multiple regression model and predicted the tes-

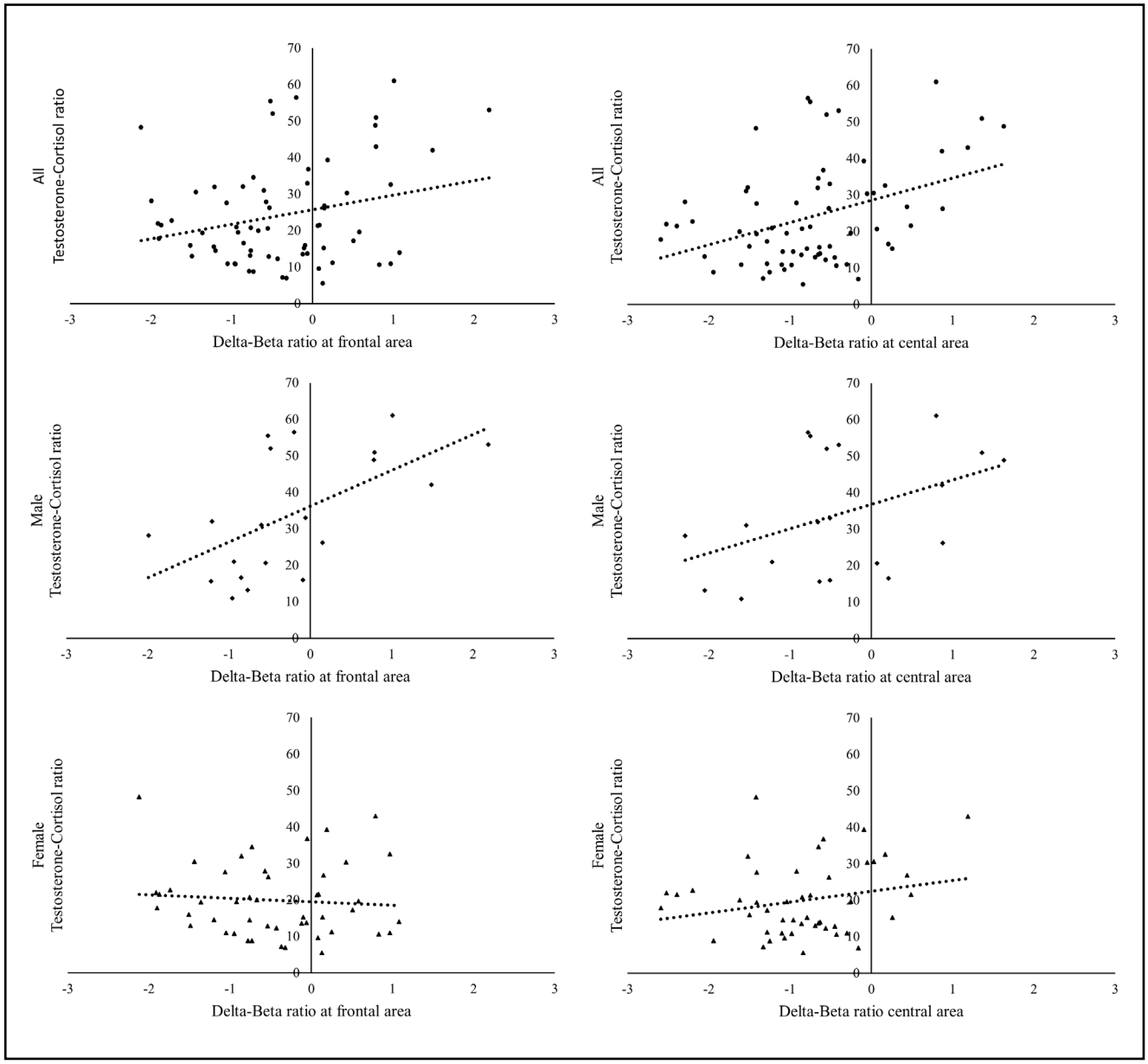

Fig. 4. Correlation of the testosterone/cortisol ratio with the resting state EEG delta/beta ratio in all participants, males and females.

tosterone/cortisol ratio as 32.0% in males and 11.9% in females. In females, the levels of estrone, estradiol, progesterone, follicle-stimulating hormone and luteinizing hormone were correlated with EEG parameters in depression patients (Silvia *et al.* 2012). Moreover, short-term transdermal administration of estrogen and testosterone to postmenopausal women affects the EEG dimensional complexity (Rosemarie *et al.* 2003). Previous study shows that ovarian hormones levels in females affect brain activity. Thus, investigating ovarian hormones levels in females will clarify our understanding of the effects of hormone levels on brain activity.

Importantly, the recent studies show that the resting state EEG delta/beta ratio is associated with physiological, psychological and hormones. An increased resting state EEG delta/beta ratio is associated with anxiety (Gennady *et al.* 2006; Miskovic *et al.* 2010a; Gennady 2011), uncertainty (Gennady *et al.* 2005), social phobia (Miskovic *et al.* 2010b), attention bias toward threat (Putman 2011) and high basal cortical levels (Dennis & Jack 2005). In contrast, a decreased resting state EEG delta/beta ratio is associated with obsessive compulsive disorder, aggressiveness, social anxiety therapy (Miskovic *et al.* 2011) and high testosterone level (Dennis & Jack 2004; Miskovic & Schmidt 2009). Thus, the resting state EEG delta/beta ratio is a possible biomarker of physiological and psychological distress.

Some limitations of this study must be considered, including the number of participants, gender and age range. The study did not test stress and depression symptoms or cognitive impairment, which can also cause imbalances of hormone levels and brain activity.

CONCLUSION

This study revealed that the testosterone/cortisol ratio is associated with the resting state EEG delta/beta ratio and that the resting state EEG delta/beta ratio at the frontal and central areas in elderly people can be used to estimate the testosterone/cortisol ratio. Thus, the resting state EEG delta/beta ratio can be used as a possible biomarker of physiological and psychological distress. A high resting state EEG delta/beta ratio is associated with a high testosterone/cortisol ratio, whereas a low resting state EEG delta/beta ratio is associated with a low testosterone/cortisol ratio. Future studies that include ovarian hormone levels in female participants may improve this non-invasive approach for estimating hormone levels by EEG measurements and our understanding of the effects of hormone levels on brain activity.

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