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Serotonin Modulates the Correlations between Obsessive-compulsive Trait and Heart Rate Variability in Normal Healthy Subjects: A SPECT Study with [^{123}I]ADAM and Heart Rate Variability Measurement

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Objective: The impact of serotonergic system on obsessive-compulsive disorder (OCD) is well studied. However, the correlation between OC presentations and autonomic nervous system (ANS) is still unclear. Furthermore, whether the correlation might be modulated by serotonin is also uncertain.
Methods: We recruited eighty-nine healthy subjects. Serotonin transporter (SERT) availability by [^{123}I]ADAM and heart rate variability (HRV) tests were measured. Symptoms checklist-90 was measured for the OC presentations. The interaction between HRV and SERT availability were calculated and the correlation between HRV and OC symptoms were analyzed after stratified SERT level into two groups, split at medium.
Results: The interactions were significant in the factors of low frequency (LF), high frequency (HF), and root mean square of successive differences (RMSSD). Furthermore, the significantly negative correlations between OC symptoms and the above HRV indexes existed only in subjects with higher SERT availability.
Conclusion: OC symptoms might be correlated with ANS regulations in subjects with higher SERT availability.

KEY WORDS: Autonomic nervous system; Heart rate variability; Obsessive compulsive symptoms; Serotonin transporter availability.

INTRODUCTION

Obsessive-compulsive disorder (OCD) presented as obsessive thought or compulsory behavior disturbed subjects' life. The prevalence rates of the OCD and associated disability were well studied in previous literatures [1]. Also, studies have shown such symptom dimensions continuous in healthy population without psychiatric disorder, which is termed obsessive-compulsive (OC) traits. Though less severe, OC traits do cause significant degree of distress [2], and its prevalence was reported to be approximately 5−13% among general populations [3-5], greatly higher to the prevalence reported in OCD.

Previous studies of OCD have highlighted the role of serotonin system and the cortico-striato-thalamo-cortical (CSTC) circuits. Following the indirect pharmacological evidence, studies have worked on serotonin transporter (SERT), which represents the pharmacological target of serotonin reuptake inhibitors (SRIs) [6]. Some studies using the tracer [^{123}I] found reduced SERT availability in OCD patients [7,8], but the results were inconsistent [9]. Furthermore, recent studies using highly SERT-selective radiotracers such as [^{11}C] DASB revealed significant reductions in SERT availability in the prefrontal-basal ganglia-thalamic-prefrontal circuits in patients with OCD compared to healthy controls [10]. Also, there was neg-

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ative correlation found between SERT availability and OC symptoms severity measured by Yale-Brown Obsessive-Compulsive Scale [11,12]. However, subclinical OC traits has hardly been studied, and to our knowledge, there was only one study investigated the psychopathology using the voxel-based morphometry (VBM) [13], which found volume changes over the corticostriatal-limbic structures. The role of serotonin system in OC traits is still unclear.

Furthermore, heart rate variability (HRV) has been used extensively to measure autonomous nervous system (ANS) function as a convenient and noninvasive indicator [14]. Previous studies found various links between HRV and psychological functions, that high frequency (HF) HRV correlates with various positive psychological adjustment outcomes, HF-HRV negatively correlated with mentally perceived stress [15], and abnormally low resting HF-HRV is associated with internalizing and externalizing psychopathology, and with a wide range of psychopathological syndromes [16]. Anxiety disorders, for example, were especially well studied by reductions in time domains and HF [17]. However, OCD subjects in previous two studies showed inconsistent reporting on HRV changes [18,19], and one study showed that the correlation has been related to the use of psychotropic medications. The correlation between drug naïve OC traits and ANS is still unclear.

There has been reported correlation between serotonin system and the ANS system [20-24]. And our previous study has revealed possible correlations between ANS functions and serotonergic activities in normal healthy subjects [25]. We assumed that these correlations might be also applied in subclinical OC (or OC traits) subjects as well. Therefore, by using symptoms checklist-90 (SCL-90) OC subscales measurement, we aim to investigate whether there's correlation between autonomic nervous system change and OC traits in healthy volunteers, and to figure out possible role of serotonin system that modulate HRV and OC symptoms.

METHODS

Subjects

Eighty-nine healthy controls (aged 18－65 years) were recruited from the community using advertisements for various studies [26-30]. The Chinese version of the Mini International Neuropsychiatric Interview [31] was admistered by an experienced psychiatrist to exclude any possible psychiatric disorders. Evaluation for other medical or neurological problems was checked by a physician. We excluded pregnant or nursing women, subjects with medical or mental illness during evaluation, subjects with drug/alcohol abuse in the past six months, and subjects receiving antidepressants, benzodiazepines, antihistamines, or beta-adrenergic antagonists. Besides, participants did not use alcohol, nicotine, or caffeine before the study for at least one day.

After the procedures fully explained, all participants provided informed consent. The local ethical committee for human research at the National Cheng Kung University Hospital approved the study protocol (no. HR-96-59).

Symptoms Checklist-90

This study used the symptom checklist-90-revised (SCL-90-R, published by the Clinical Assessment division of the Pearson Assessment & Information group), a reliable and validated scale [32,33]. The checklist assesses the following 9 primary psychological symptoms: somatization, obsessive-compulsion (O-C), interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation, and psychoticism. The reliability and validity were well established, as well as in Taiwan [34]. Only the O-C subscale was utilized in this study.

SERT Availability in the Midbrain

The procedure of the SPECT examination was identical to our previous studies [25]. Brain SPECT imaging would be applied after an intravenously injection of 185 MBq (5 mCi) of [^{123}I]ADAM. Reconstruction of the images would utilize Butterworth and Ramp filters (cut-off frequency = 0.3 Nyquist; power factor = 7) with attenuation by Chang's method [35]. The [^{123}I]ADAM SPECT images, acquired at 240 minutes after injection, were utilized to assess SERT availability because studies have validated this imaging time and its feasibility to determine SERT in the midbrain [36,37]. All the SPECT images would be co-registered with the corresponding T2-weighted MRI image automatically and was then finely-adjusted manually by an experienced nuclear medicine physician who was blind to the participants' clinical data by PMOD software (PMOD Technologies Ltd., Zurich, Switzerland). For co-registration, rigid transformations were defined by 6

parameters, the rotation angles and the translation distances in the three spatial directions. The SERT availability, expressed as the specific uptake ratio, was calculated as the average count in the midbrain region of interest (ROI) minus the average count in the cerebellum ROI divided by the average count in the cerebellum ROI.

HRV Measurement Autonomic Nervous System Activity

All the procedures were also identical to our previous study [25]. Subjects were asked to relax and rest in a comfortable and quiet room before the HRV measurements. Time domain index, root mean square of successive differences (RMSSD) were calculated. Power spectral density analysis of HRV was performed by fast Fourier transformation [38]. Several spectral components are defined as follows: low frequency (LF) (0.04 to 0.15 Hz), HF (0.15 to 0.40 Hz) and total power (≤ 0.4Hz). Because the skewness of HRV, ln-transformation was performed for following analyses.

Statistical Analysis

Independent *t* tests and chi-square tests were used to test the differences between low and high SERT availability groups, split at medium (2.15). Because age was significantly different between groups, age was controlled in the following analyses.

Two-way analysis of covariance (ANCOVA) was used for testing the interaction between HRV and SERT availability/SERT group on the results of obsessive-compulsion subscale. Partial correlations, as post-hoc analyses controlling for age [39], were used to examine the correlations between HRV and obsessive-compulsion subscale under different groups. Because anxiety might affect HRV and serotonin vulnerability [40], anxiety score in SCL-90 was further controlled in the model.

The data were analyzed using Statistical Package for Social Science software version 20 (IBM Co., Armonk, NY, USA). The threshold for statistical significance was set at $p < 0.05$.

RESULTS

Table 1 showed the demographic data, the scores of SCL-90 and each HRV indexes of the healthy subjects. When stratified all these data to two groups with low and

Table 1. Demographic data and comparison of low and high group of SERT availability

Variable	Total (n = 89)	Low (n = 44)	High (n = 45)	Statistic	
				t/χ^2	*p* value
Age	34.35 ± 12.37	38.89 ± 13.71	29.90 ± 9.01	3.67	< 0.001
Sex (M/F)	40/49	19/25	21/24	0.11	0.74
SCL-90					
Anxiety	1.91 ± 2.80	2.16 ± 3.31	1.67 ± 2.21	0.83	0.41
Depression	4.25 ± 5.24	4.73 ± 5.50	3.78 ± 4.99	0.85	0.40
Phobic anxiety	0.97 ± 1.58	1.20 ± 1.77	0.73 ± 1.34	1.42	0.16
Somatization	4.25 ± 4.55	4.77 ± 4.70	3.73 ± 4.39	1.08	0.28
Obsessive-compulsion	6.02 ± 4.77	6.41 ± 4.95	5.64 ± 4.61	0.75	0.45
Interpersonal sensitivity	3.01 ± 3.43	2.77 ± 3.26	3.24 ± 3.61	−0.65	0.52
Hostility	1.56 ± 2.08	1.73 ± 2.32	1.40 ± 1.84	0.74	0.46
Paranoid ideation	1.65 ± 2.11	1.82 ± 2.51	1.49 ± 1.63	0.74	0.46
Psychoticism	1.81 ± 2.96	2.11 ± 3.17	1.51 ± 2.74	0.96	0.34
ln (LF)	5.93 ± 0.86	5.78 ± 0.95	6.08 ± 0.75	−1.66	0.10
ln (HF)	5.41 ± 1.04	5.20 ± 1.14	5.61 ± 0.91	−1.86	0.07
ln (LF/HF)	0.52 ± 0.61	0.57 ± 0.67	0.47 ± 0.54	0.82	0.42
ln (total power)[a]	7.14 ± 0.78	6.97 ± 0.87	7.31 ± 0.64	−2.09	0.040
ln (RMSSD)	0.59 ± 0.53	0.51 ± 0.57	0.66 ± 0.47	−1.32	0.19
SERT availability	2.20 ± 0.52	1.79 ± 0.30	2.61 ± 0.34	−12.02	< 0.001

Values are presented as mean ± standard deviation or number only. Low and high groups of SERT were split at medium (2.15).
SERT, serotonin transporter; SCL-90, symptoms checklist-90; LF, low frequency; HF, high frequency; RMSSD, root mean square of successive differences.
[a]After controlling age, ln (total power) is not significant between group ($p = 0.38$).

high SERT availability (divided at medium 2.15), there was only significant difference over age, total power, and SERT availability. After controlling age, total power is not significant between group ($p = 0.38$).

Interaction analysis showed significant interaction between HRV and SERT availability on obsessive-compulsion subscale. The factors included LF, HF, and RMSSD. The *post-hoc* analyses, partial correlations, showed that the above mentioned HRV factors and obsessive-compulsion subscale were negatively correlated only in the group with high SERT availability (Table 2). Although we found significant correlation between the anxiety subscale and the obsessive-compulsion subscale of SCL-90 ($r = 0.76$, $p < 0.001$), the results of partial correlations, controlling for age and anxiety, revealed less significant but still negative correlation between HF and obsessive-compulsion subscale in the group with high SERT availability ($r = -0.34$, $p = 0.02$).

DISCUSSION

Few studies focused on correlations between serotonin, HRV changes and OC presentation. In our study, we found that in healthy subjects, there's significant interaction in SERT availability and obsession with HRV factors of LF, HF, and RMSSD. Furthermore, when divided SERT availability into high and low availability group we found obsessive-compulsion subscale negatively correlated with LF, HF, total power, and RMSSD.

We found significant interaction between the HRV and obsessive-compulsion subscale, and SERT availability level would alter the negative correlation between HRV and obsessive-compulsion subscale, in terms of LF, HF, total power, and RMSSD. Previous studies showed that levels of serotonin is correlated with OC symptoms severity [11,12] and also autonomic systems [20,25]. Our study noticed that the correlations between OC symptoms and HRV only exist in higher SERT group. The results may indicate that serotonergic systems may modulate the correlations between ANS functions and OC symptoms, though the exact mechanism underlying needs further study to verify. When serotonergic level is inadequate, the modulatory effect may be impaired. Moreover, the clinical meaning of lower SERT availability and its implication on central serotonergic system activity remains uncertain and still under investigation. But in our result showed on OC traits subjects, we noticed that the correlations between OC symptoms and SERT would be vanished in subjects with lower SERT availability, which may indicate poorer modulation abilities of serotonergic activities and thus diminished correlation with HRV. Our results could partially explain previous findings on OCD subjects with HRV change, that Slaap *et al.* [19] found no HRV change and Pittig *et al.* [18] found lower HRV but might be related to the use of current psycotropics use. We suspected that in subjects with lower SERT availability, the modulation between autonomic function and obsessive symptoms seemed much weaker. And in such condition, SRIs, which re-models the serotonin system, may take roles in treating the obsessive symptoms and ameliorate anxiety symptoms in OC subjects [41,42]. There's also one study [43] using α-[^{11}C]methyl-L-tryptophan brain trapping constant as a measure of serotonin synthesis capacity, supported that increased serotonergic tone may associated with successful improvement of OCD symptoms with either sertraline treatment or

Table 2. Interactions between HRV and SERT availability on obsessive-compulsion subscale and partial correlation between HRV and obsessive-compulsion subscale in low and high group of SERT availability

Variables in HRV	Interaction[a]		Low (n = 44)		High (n = 45)	
	F	*p* value	*r*[b]	*p* value	*r*[b]	*p* value
ln (LF)	4.33	0.041	−0.01	0.945	−0.36	0.016
ln (HF)	4.97	0.028	−0.06	0.707	−0.46	0.002
ln (LF/HF)	1.11	0.295	0.08	0.618	0.26	0.091
ln (total power)	3.44	0.067	−0.08	0.626	−0.35	0.021
ln (RMSSD)	4.79	0.031	−0.01	0.948	−0.44	0.003

Low and high groups of SERT were split at medium (2.15). Age was controlled in these analyses.
HRV, heart rate variability; SERT, serotonin transporter; LF, low frequency; HF, high frequency; RMSSD, root mean square of successive differences.
[a]Theresults were similar if SERT availability group was used instead of SERT availability level. [b]The results were similar if Spearman's rho correlation was used.

cognitive behavioral therapy. Besides, recent study also demonstrated possible different pathology in early-onset OCD, with more hereditary, unaltered SERT availability comparing to late-onset OCD [44], and worse response to selective serotonin reuptake inhibitors (SSRIs) [45,46]. However, further study will be needed to compare subjects with OC traits with normal healthy control and OCD patients.

Furthermore, our previous study [40] has found that baseline anxiety ratings positively correlated with post-tryptophan depletion changes in sympathetic nervous activity and negatively correlated with post-tryptophan depletion changes in parasympathetic nervous activity. It showed relationship between subjective anxiety rating, serotonin, and HRV. In our study, our subjects revealed no significant difference in SCL-90 anxiety scores. And considering anxiety as possible confounding factor, we additionally examined our results, which found less significance but still negative correlation between obsessive score and HF in the group of higher SERT availability.

Another interesting finding is that the directions of correlations of LF and HF are consistent, which is inconsistent in some previous HRV studies [47]. However, recent studies have challenged the interpretation of the LF as indices of sympathetic cardiac control, and suggested that HRV power spectrum, including LF component, is mainly determined by the parasympathetic system [48]. Therefore, parasympathetic function might play a crucial role in ANS function to modulate symptoms related to an altered serotonin level [49].

Besides serotonin, recent researches about OCD have extended some emphasis on dopamine and glutamate system [1]. Evidences have demonstrated in OCD there's significant reduction of D_2 receptors in striatum [50] and D1 binding potential in anterior cingulate cortex [51]. Our previous study worked on the relationship between striatal dopaminergic system and cardiovascular activity has shown that the ratio of the radioactivity in the striatum and the frontal cortex, indicated striatal D_2/D_3 receptor binding, correlated positively with LF power in healthy subjects [52]. In our study, however, when adjusted with age and SCL-90 anxiety score, the correlation between OC score and LF got diminished. As for glutamate research on OCD [53], while glutamate plays a crucial role in CSTC circuits, enhanced glutamate turnover was correlated with reduction in OC symptoms following treatment. Though glutamatergic inputs were considered to be related with sympathetic activation, with rapid increase in blood pressure and heart rate after injection of monosodium glutamate in the paraventricular nucleus [54], there was limited study focused on this association. Due to the limitation in our study design, the role of dopamine and glutamate system on cardiovascular activity in OCD needs further examination.

Our results must be interpreted with caution because of potential limitations with relatively small sample size, the lack of assessment of body mass index [55] and exercise behaviors which could influence the ANS and SERT availability. Also, the cross-sectional correlation study design could not confirm a causal relationship between the obsession and ANS, and this model of SERT-obsession-ANS associations may be over-simplified. And, to deal with the possible covariant anxiety and perceived stress level [15], self-ratings of perceived emotional stress, and scales other than SCL-90, such as Hamilton Anxiety Rating Scale would be needed. Finally, there may be other factors or other monoamines playing roles in this model. Our findings mandate further confirmation and challenge tests.

The current study showed the possible correlations between OC symptoms and ANS functions under serotonergic modulation. Besides serotonergic system related to HRV and OC scores, dopamine may play another important role of biomarker in their correlations with HRV [52]. More potential biomarker such as hypothalamic-pituitary-adrenal axis and even neurocognition variations may alter the progressions of OC symptoms [56]. This may help us a more integrative view of the pathogenesis of OC spectrum disorder and manage the symptoms according to different potential biomarkers. Further study may apply this hypothetical model in OCD patients to corroborate our result. In addition, research upon HRV change before and after SSRI intervention may also be needed.

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■ Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

■ Author Contributions

Study design: Wei Hung Chang, Nan Tsing Chiu, Yen Kuang Yang. Writing the protocol: Wei Hung Chang. Data collection: Kao Chin Chen, I Hui Lee, Yen Kuang Yang, Wei Hung Chang. Statistical analysis: Huai-Hsuan Tseng, Po See Chen. Writing—original draft: Che Yu Kuo. All authors interpreted the analysis of the results and helped to revise the manuscript.

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