Correlation between Morphologic Changes and Autism Spectrum Tendency in Obsessive-Compulsive Disorder

（強迫性障害における自閉傾向と脳の形態学的変化との関連）

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Abstract

Objectives: Obsessive-compulsive disorder (OCD) is one of the most debilitating psychiatric disorders, with some speculating that a reason for difficulty in its treatment might be its coexistence with autism spectrum. We investigated the tendency for autistic spectrum disorders (ASD) in patients with OCD from a neuroimaging point of view using voxel-based morphometry.

Methods: We acquired T_1-weighted images from 20 patients with OCD and 30 healthy controls and investigated the difference in regional volume between the groups as well as the correlation between Autism-Spectrum Quotient (AQ) scores and regional cerebral volumes of patients with OCD.

Results: Volumes in the bilateral middle frontal gyri were significantly decreased in patients with OCD compared to controls. Correlational analysis showed significant positive correlations between AQ scores and regional gray matter (GM) volumes in the left dorsolateral prefrontal cortex (DLPFC) and left amygdala. Furthermore, GM volumes of these regions were positively correlated with each other.

Conclusions: The positive correlation of ASD traits in patients with OCD with regional GM volumes in the left DLPFC and amygdala could reflect the heterogeneity of patient symptoms. Our results suggest that differences in GM volume might allow classification of patients with OCD for appropriate therapy based on their particular traits.

Keywords: obsessive-compulsive disorder (OCD), autism spectrum disorder (ASD), Autism-Spectrum Quotient (AQ), voxel-based morphometry (VBM)

Introduction

Obsessive-compulsive disorder (OCD) is characterized by distressing, intrusive obsessive thoughts and/or repetitive compulsive physical or mental acts. The lifetime prevalence of OCD is reported as one to 3 percent, making it the fourth most common psychiatric disorder (1), and the World Health Organization has ranked OCD as one of the most debilitating disorders (2). Some speculate that its coexistence with autism spectrum might be a reason for the difficulty in treating OCD. Bejerot identified autistic traits in 20 percent of subjects with OCD and suggested that the comorbidity produces a more severe and treatment-resistant form of OCD and that OCD with comorbid autistic spectrum disorder (ASD) should be recognized as a valid OCD subtype, analogous to OCD with comorbid tics (3). On the other hand, Lai's group reported OCD symptoms in 7 to 24 percent of patients with ASD (4).

One well known screening tool of ASD is the Autism-Spectrum Quotient (AQ) developed by Baron-Cohen and colleagues (5). Cath's group reported that autism-related problem behaviors differ between patients with OCD with comorbid ASD and patients with pure OCD and suggested the assessment of specific autism symptom domains and fine-tuning of treatment for patients with OCD with ASD (6).

Neuroimaging techniques have unveiled the morphological and functional changes related to OCD and ASD. In OCD, the focus has been on the cortico-striatal circuitry, but recent studies show the involvement of several regions, including the lateral and medial orbitofrontal cortices, dorsal anterior cingulate cortex, and amygdalocortical circuitry (7). In ASD, altered structure or functions have been reported in regions related to social perception and cognition, the social brain, and executive function (4). Interestingly, the frontostriatal circuit is involved in both OCD and ASD. The Medical Research Council of the United Kingdom's Autism Imaging Multicentre Study (MRC AIMS) Consortium has suggested the possible overlap of abnormalities in the fronto-striatal-thalamic circuitry that mediate some of the repetitive behaviors in ASD with mediating symptoms observed in people with OCD (8).

Several reports have investigated the structural abnormality of OCD and ASD using voxel-based morphometry (VBM). A meta-analysis reported that patients with OCD showed reduced GM in the parietofrontal cortical regions, including the supramarginal gyrus, dorsolateral prefrontal cortex (DLPFC), and orbitofrontal cortex, and increased GM in the putamen and anterior prefrontal cortex (9). In contrast, VBM meta-analyses of ASD have brought controversial results. In ASD, Nickl-Jockschat and associates reported disturbances in several regions, including the lateral occipital lobe, pericentral region, medial temporal lobe, and basal ganglia and proximate to the right parietal operculum (10), and Via and associates found robust

decreases in GM volume in the bilateral amygdala-hippocampus complex and the bilateral precuneus as well as a small increase in the middle-inferior frontal gyrus (11). Though the sample sizes of both meta-analyses were sufficient (277 patients with ASD and 303 controls [10]; 496 patients with ASD and 471 controls [11]), their results were totally different, which may be attributable to their different statistical approaches (activation likelihood estimation [ALE] [12] and signed differential mapping [SDM] [13]).

Though we see some overlapped regions between ASD and OCD, little is known about the association between these 2 disease entities. Therefore, we examined the ASD tendency of patients with OCD from the point of view of neuroimaging. We employed the Japanese version of the AQ (14,15) as an index for ASD tendency and the regional GM volume by VBM as an index for the neural basis and then explored the relationship between the two. We wanted to understand how the tendency for ASD affects the neural basis of OCD, so we focused on previously reported (7) regions associated with OCD, i.e., the fronto-striatal circuits and amygdala, and hypothesized that the AQ score might be related to these regions.

Methods

Participants

The subjects were 20 patients aged 18 to 48 years diagnosed with OCD (based on the criteria of the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders* [DSM-IV-TR] (16) and 30 healthy volunteers matched for age, gender, and handedness who underwent magnetic resonance (MR) imaging at Chiba University Hospital.

Patients were primarily diagnosed with OCD using the Structured Clinical Interview for DSM-IV Axis I Disorders, Research Version, Patient Edition. (SCID-I/P) (17). We excluded those with past or current diagnosis of comorbid schizophrenia or substance-related disorders, total intelligence quotient (IQ) under 80, score below 17 on the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) (18) (for patients with OCD), or a clinically significant general or neurological disease that might influence the structural brain image, patients currently pregnant or nursing, or those with any contraindication for MR imaging, such as a pacemaker.

The Research Ethics Committee of Chiba University Hospital approved all procedures, and participants provided informed consent after receiving a complete description of the study.

Clinical measurements

All patients were assessed for severity of OCD symptoms using the Japanese version of Y-BOCS, and all participants completed the self-administered AQ questionnaire, which was developed to quantify autistic traits in individuals with normal intelligence. We adopted the Japanese version of the AQ scale (14) to measure the autistic tendencies of individuals. AQ is not a diagnostic measure, and no one had a clinical diagnosis of ASD. Scores of all items were tallied, and a high AQ score indicated a high autistic load near the autistic end of the autism spectrum.

MR imaging acquisition and image processing

At Chiba University, all subjects underwent 3-dimensional (3D) T_1-weighted imaging using an MR scanner equipped with a 32-channel phased-array head coil (Discovery MR750 3.0T, General Electric Healthcare, Waukesha, WI, USA). Images were collected by 3D spoiled gradient recalled acquisition in steady state (SPGR) sequence (echo time, 3.164 ms; repetition time, 8.124 ms; flip angle, 15°; acquisition matrix, 256 × 256; slice thickness, one mm; field of view, 25.6 cm; number of excitations, one; bandwidth, 31.25 kHz; inversion time, 420 ms; acceleration factor, 2).

T_1-weighted MR images were processed using Statistical Parametric Mapping 8 (SPM8) software (Wellcome Institute of Neurology, University College London, UK, http://www.fil.icon.ucl.ac.uk/spm) running under MATLAB® R2012b (The MathWorks, Inc., Natick, MA, USA). The images were preprocessed using the VBM8 toolbox (http://dbm.neuro.uni-jena.de/vbm/), which is an extension of the unified segmentation model that consists of spatial normalization, bias field correction, and tissue segmentation (19). Registration to the stereotactic space of the Montreal Neurological Institute (MNI) consisted of linear affine transformation and nonlinear deformation using high dimensional diffeomorphic anatomical registration through exponential Lie algebra (DARTEL) normalization (20). The normalized and segmented images were modulated by applying a nonlinear deformation, which allows comparison of absolute amounts of tissue corrected for individual differences in brain size. Bias-corrected, modulated, and warped tissue maps were then written with an isotopic voxel resolution of 1.5 × 1.5 × 1.5 mm and smoothed with an 8-mm full width at half maximum (FWHM) Gaussian kernel.

Statistical analysis

Statistical analysis was performed with SPM8, which implemented a general linear model. First, we performed a 2-sample t-test to detect the difference in GM volume between patients

with OCD and controls. Hypothesizing an influence of ASD tendency on the neural basis of OCD, we treated the total AQ score as a covariate. The initial voxel threshold was set to $P < 0.001$ uncorrected. Clusters were considered significant that fell below a cluster-corrected false discovery rate (FDR), q = 0.05. Then, we used a multiple regression model to analyze the correlation between AQ score and regional GM volume. We treated age, gender, Y-BOCS score, and AQ score as covariates. Because regression analysis between Y-BOCS and AQ score resulted in low r-squared values (-0.204, $P = 0.388$), we considered them independently from each other. Because the regions of interest (ROI) included small regions, such as the amygdala, we performed ROI analysis using PickAtlas software (21), employing its automated anatomical labeling (AAL) atlas to generate the ROIs. Based on our hypotheses, we made a fronto-striatal ROI that included the bilateral frontal lobes, caudate nuclei, and putamina and a second ROI that consisted of the bilateral amygdalae. Significance levels were set at family-wise error (FWE)-corrected $P < 0.05$. We obtained MNI coordinates to detect the anatomical region of the clusters.

Results

Nine of 29 patients identified with OCD met the study's exclusion criteria, so we analyzed the remaining 20 patients and 30 controls. Table 1 shows demographic data of the subjects. The mean duration of OCD in patients was 11.5 ± 7.5 years, the mean score of Y-BOCS was 26.2 ± 3.7, and the mean score of AQ was 27.2 ± 6.7. Fifteen of 20 patients (75%) were prescribed antidepressants, antipsychotics, or anxiolytics. However, adherence was generally poor, and we could not assess the real dose.

Group comparison revealed significantly decreased volume in the bilateral middle frontal gyri in patients with OCD compared to controls (Fig. 1, Table 2). We found significant positive correlations between AQ score and regional GM volume in the left DLPFC (peak MNI coordinates: x, −42; y, 38; z, 22; cluster size, 71; Fig. 2a) and left amygdala (peak MNI coordinates: x, −26; y, −4; z, −24; cluster size, 103; Fig. 2b) in patients with OCD. To examine the strength of the correlation between these 2 regions, we extracted GM volumes from each cluster and performed correlational analysis, which demonstrated their moderate correlation with each other (Fig. 3; r = 0.53, $P = 0.02$). We found neither significant negative correlation between AQ scores and regional GM volumes nor any correlation between AQ and regional GM volumes in controls.

Discussion

We investigated the regional reduction in GM volume of patients with OCD as well as the relationship between the ASD tendency of OCD patients and regional GM volumes. Our results revealed that patients with OCD showed decreased GM volumes in the prefrontal regions. We also found a positive correlation between AQ scores and GM volumes in the left DLPFC and left amygdala.

Previous studies have reported GM reduction in OCD in several regions and commonly in the frontal areas (9,22), which were consistent with our result. On the other hand, we did not find altered volume in the basal ganglia or anterior cingulate, which has often been reported. This might be explained by the limited sample of our study. Indeed, lowering the statistical threshold, for example, to $P < 0.01$ uncorrected for multiple comparisons, resulted in reduced volumes in these regions. In other words, volume reduction in the bilateral prefrontal cortices is more meaningful in patients with OCD when considering AQ. We also found a positive correlation between AQ scores and GM volumes in the DLPFC and amygdala. Morgan and colleagues reported an increase in the microglia in the DLPFC in patients with ASD, which led to increased regional volume in the DLPFC (23). Geurts and associates also reported the positive correlation of ASD severity with the middle frontal gyrus (24) The DLPFC is well known as a center of executive function, and ASD shows executive dysfunction (25). The DLPFC is also related to social learning (26) and can thus modulate the behavior of subjects with autistic tendency. Considering that the AQ score is a useful tool for screening ASD (5) and that the AQ is high in patients with OCD with ASD (27). Our results suggest that the regional GM volume of the DLPFC is relatively preserved in patients with OCD with ASD tendency.

Besides the DLPFC, we also found a positive correlation between the AQ score and regional GM volume in the amygdala. Our results may seem to contradict Via's results (11), which showed decreased gray matter volume in the amygdala-hippocampus complex in ASD. However, if we lower the statistical threshold, for example, to $P < 0.001$ uncorrected for multiple comparisons, group comparison shows volume reduction in the amygdala-hippocampus complex of patients with OCD compared to controls. Taking this into consideration, the GM volume of the amygdala showed a positive correlation with AQ score though it was decreased compared to that in controls.

In addition, some controversial findings are reported. Murphy's team reported a significantly larger volume of the amygdala in patients with ASD (28), and Dichter's group demonstrated hyperactivation in the bilateral amygdala during face anticipation that predicted social symptom severity (29). Those findings with ours indicate that ASD is related to altered structure or function of the amygdala, which could contribute to the severe depressive or

pervasive anxiety shown by patients with OCD with ASD traits (30). In this context, classification of patients with OCD based on differences in structural GM volume could optimize therapy planning according to their individual traits.

We also found a positive correlation between GM volumes of the left amygdala and DLPFC. St. Onge and colleagues found that prefrontal-amygdala circuits are related to risk-based decision-making (31). Ghashghaei's group suggested synergistic roles of the amygdala and prefrontal cortex in regulating purposive behavior, with the amygdala extracting the affective significance of stimuli and the prefrontal cortex guiding goal-directed behavior (32). These functions are essential in judging rewarding or aversive outcomes of actions, which could modulate the behavior characteristics of patients with OCD. In addition, the MRC AIMS Consortium reported increased volume in the DLPFC of adults with ASD and correlation of several regions, including the amygdala and prefrontal region, as a network (8). Taken together, these findings suggest that both OCD and ASD tendency might share common neural networks, including the prefrontal circuit.

Our study has some limitations. First, our sample size was relatively small, and larger samples are needed to confirm our findings. Second, we employed the AQ as an index for ASD tendency, and tough the AQ is easy to use and validate, it is determined by a self-administered questionnaire and is thus subject to the individual's perspective. From this point of view, other assessment tools, such as the Autism Diagnostic Interview-Revised (33), might be more accurate for assessing the ASD tendency of subjects. Third, we did not fully assess depression or anxiety symptoms of subjects and so could not exclude the influence of depression or anxiety in the statistical model.

Conclusions

In conclusion, we found the positive correlation of ASD traits in patients with OCD with regional GM volumes in the left DLPFC and amygdala, which could contribute to the heterogeneity of symptoms of patients with OCD. Our results suggest that classification of patients with OCD based on differences in GM volume could optimize therapy planning based on their individual traits.

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Table 1. Demographics of subjects

	Patients		Healthy controls		*P*-value
	Mean (SD)	Range	Mean (SD)	Range	
Age (years)	34.1 (8.5)	18-48	31.2 (8.5)	20-48	0.24
Gender (M/F)	10/10		15/15		1
Handedness (right/left)	20/0		27/3		0.15
Age at onset of OCD	22.7 (7.3)	11-35	-	-	
Duration of illness (years)	11.5 (7.5)	0-25	-	-	
Y-BOCS total score	26.2 (3.7)	20-34	-	-	
AQ total score	27.2 (6.7)	17-39	16.0（4.7）	7-25	< 0.0001

AQ, autism spectrum quotient; F, female; M, male; OCD, obsessive-compulsive disorder; SD, standard deviation; Y-BOCS, Yale-Brown Obsessive-Compulsive Scale

Table 2. Two-sample t-test between patients with obsessive-compulsive disorder (OCD) and controls

Region	Montreal Neurological Institute (MNI) coordinates			Cluster size	T-value
	x	y	z		
Left middle frontal gyrus	-36	30	42	766	5.45
Right middle frontal gyrus	44	39	31	576	4.76

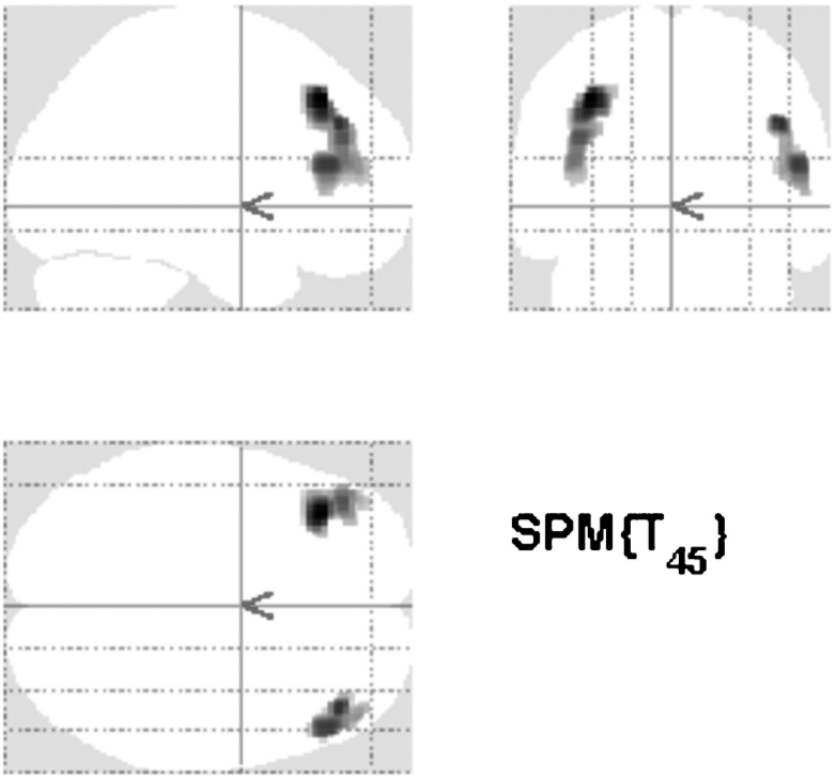

Fig. 1. Two-sample t-test between patients with obsessive-compulsive disorder (OCD) and controls. Group comparison revealed significantly decreased volumes in the bilateral middle frontal gyri of patients with OCD compared to controls ($P < 0.05$, false-discovery rate corrected for multiple comparisons at cluster level).

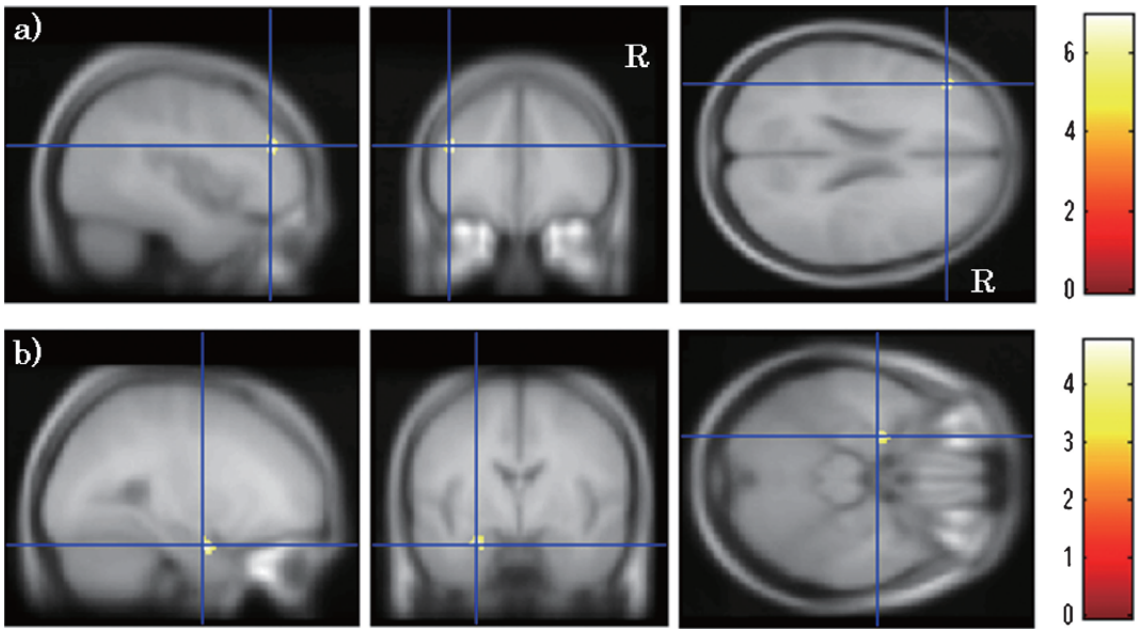

Fig. 2. Positive correlation between autism spectrum quotient (AQ) score and regional gray matter (GM) volumes. We found significant positive correlations between AQ score and regional GM volumes in the left dorsolateral prefrontal cortex (x, −42; y, 38; z, 22; cluster size, 71; Fig. 2a) and left amygdala (x, −26; y, −4; z, −24; cluster size, 103; Fig. 2b). Small volume correction (family-wise error, $P < 0.05$) was applied to each cluster to correct multiple comparisons.

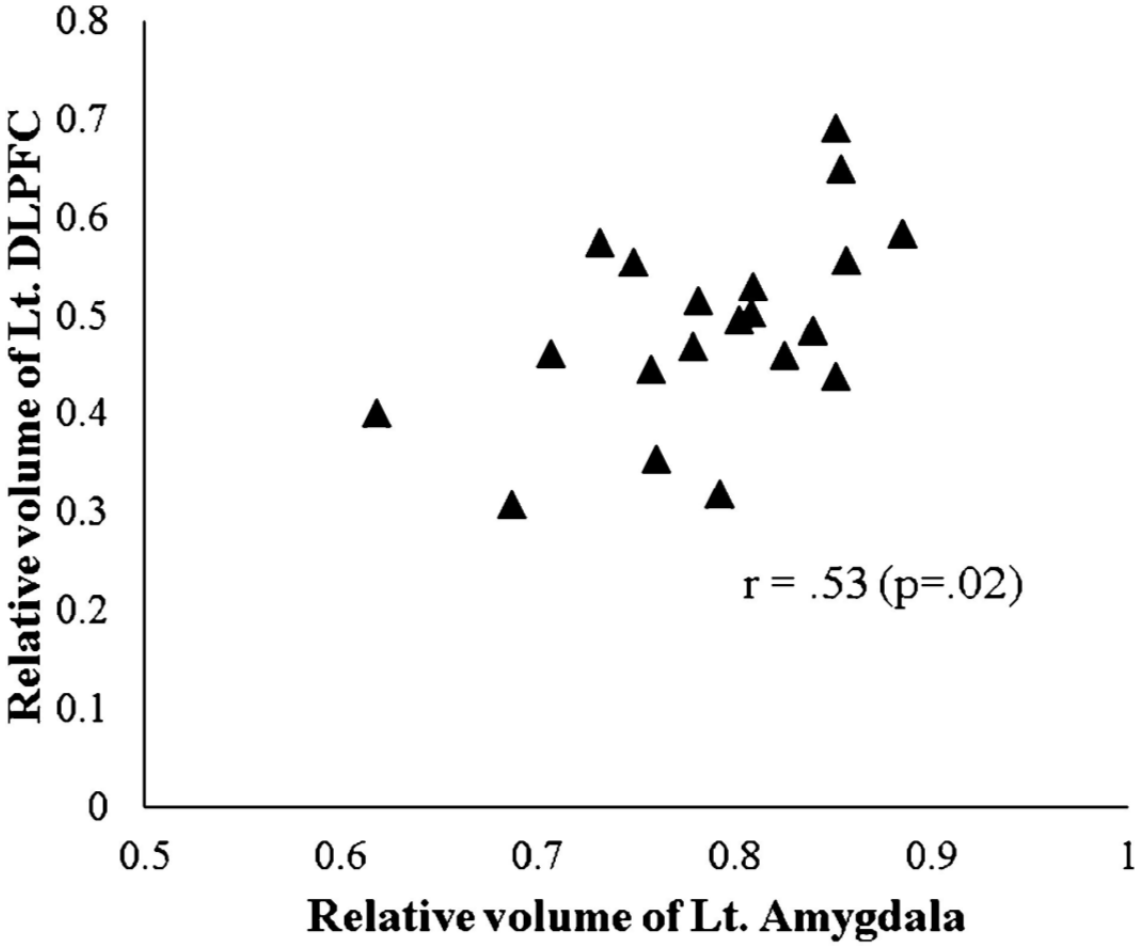

Fig. 3. Correlation between regional gray matter (GM) volumes of the left dorsolateral prefrontal cortex (DLPFC) and left amygdala. GM volumes of both the left DLPFC and left amygdala correlated with autism spectrum quotient (AQ) scores in patients with obsessive-compulsive disorder (OCD) and correlated positively with each other (r = 0.53, *P* = 0.02).