



# Relationships Between Catecholamine Levels and Stress or Intelligence

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## Abstract

Catecholamines, including epinephrine (E), norepinephrine (NE), and dopamine (DA), are associated with the response to stressful conditions. However, the relationships of catecholamines with intelligence and their interactions with stress remain unclear. This study assessed stress, intelligence quotient (IQ), and catecholamine levels in 70 healthy subjects to elucidate associations between catecholamines and stress, and between catecholamines and IQ. Additionally, the associations of catecholamines with stress and IQ were analyzed according to hemispheric dominance using the Brain Preference Indicator (BPI). There were positive correlations between the NE/E ratio and the somatization of stress but negative correlations between the E/NE ratio and the somatization of stress among the total number of subjects. In the right-brain-dominant group, a high E/DA ratio was correlated with low levels of stress, somatization and depression, and high NE/E and DA/E ratios were associated with high levels of somatization. In the left-brain-dominant group, high E levels were correlated with low levels of depression. In the total subjects, there were positive correlations between the NE/E and DA/E ratios and the sum of the vocabulary, arithmetic, picture arrangement, and block design IQ subtests. Thus, these catecholamines were associated with stress and IQ, which suggests that the autonomic functional regulation of catecholamine levels in relation to stress may also affect cognitive functions related to intelligence in the brain. Furthermore, the relationships between catecholamines and stress or IQ differed depending on hemispheric dominance, which suggests that the present results could be used to inform the development of personalized therapies based on hemispheric asymmetry.

**Keywords** Dopamine · Norepinephrine · Epinephrine · Stress · Intelligence

## Introduction

Catecholamines are derived from the amino acid tyrosine and include epinephrine (E), norepinephrine (NE), and dopamine (DA). Catecholamine-secreting cells employ several reactions to convert tyrosine serially to L-DOPA and then DA. Depending on the cell type, DA is further converted to NE or even further converted to E [1]. Catecholamines are mainly produced by chromaffin cells in the adrenal medulla and postganglionic fibers in the sympathetic nervous system. DA, which acts as a neurotransmitter in the central nervous system, is largely produced in neuronal cell bodies in two areas of the ventral tegmental area (VTA) and the substantia nigra. NE and DA also act as neuromodulators in the central nervous system and as hormones in the blood circulation system, and NE is a neuromodulator of the peripheral sympathetic nervous system and is present in the blood. E is normally produced from chromaffin cells of the adrenal medulla [2], and E neurons that contain phenylethanolamine

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*N*-methyltransferase (PNMT), the epinephrine-forming enzyme, have their cell bodies in brain stem regions [3].

Stress affects a wide variety of bodily functions, but the two most consistently activated systems are the hypothalamic–pituitary–adrenal (HPA) axis and the NE system, including the sympathetic nervous system and the locus coeruleus (LC)-centered system in the brain [4]. The neural noradrenergic system is influenced by increased exposure to corticotropin-releasing hormone (CRH), which is triggered by the stress response [5]. Repeated immobilization stress in rat induced an elevation of catecholamine production such as NE and E which may reflect the activation of sympathetic nervous system [6]. Stress also induces changes in E expression in the adrenal medulla [7], and E is a short- and long-term regulator of stress and illness development [8]. Stress plays a crucial role in the pathogenesis of several psychiatric disorders, and the DA and NE systems play important roles in the regulation of the stress response [4, 9]. Furthermore, DA neurons play critical roles in the responses to acute and repeated stress in terms of health and psychopathology [10, 11], and concomitant changes in the dopaminergic and neurotensinergic systems occur under diverse conditions of stress [12]. Dopaminergic system after stress responds in the medial prefrontal cortex (MFC) is thought to serve as a protection against positive psychotic symptoms, since the increased DA activity in the MFC suppresses limbic DA transmission [13]. Thus, stress is associated with the HPA axis and the sympathetic nervous system, and catecholamines (DA, NE, E) play important roles in the stress response.

Stress affects cognition in a number of ways, acting rapidly via catecholamines and more slowly via glucocorticoids, and catecholamine actions involve beta adrenergic receptors, whereas glucocorticoids biphasically modulate synaptic plasticity over hours and also produce longer-term changes in dendritic structure that last for weeks [14]. Catecholamine levels in the prefrontal cortex (PFC) alter the neuronal and behavioral correlates of cognitive functions, particularly for attention and working memory [15], and the integrity of the LC noradrenergic system plays a key role in determining late-life cognitive abilities [16]. Additionally, DA acts as a powerful regulator of cognitive brain function as well as in adaptations to action, emotion, and motivation [17, 18].

The influences of hemispheric lateralization are well known in terms of affective responses, emotion, language and dexterity [19], and have been shown to be beneficial for functioning [20]. Additionally, activity in the HPA axis is related to behavioral lateralization and brain asymmetry [21]. It has been reported that hemispheric lateralization is protective against the adverse effects of life events, difficulties, or acute stress on well-being [22] and may be associated with efficient stress and emotional self-regulation [23]. Furthermore, structural laterality is associated with cognition

and mood [24], and asymmetry in hemispheric volume is associated with intelligence quotient (IQ) [25].

Therefore, the present study investigated the associations between catecholamine levels and stress including three simplified stress factors of somatization, depression, and anger, and then examined the correlations between catecholamine levels and IQ in healthy individuals with no history of neuropsychiatric conditions. Subsequently, these relationships were analyzed according to right and left hemispheric dominance.

## Method

### Subjects

Seventy healthy subjects were recruited through internet advertisements. They were incentivized with about USD \$28 of money. The male/female ratio was recruitment balanced. In the present study, the stress, IQ, and catecholamine levels of 70 healthy subjects were assessed; five subjects did not respond to the Stress Response Inventory (SRI) and one subject did not respond to the Brain Preference Indicator (BPI). One sample in the measurement of DA levels was a measurement error, so the one was excluded only in the DA data. The Structured Clinical Interview for the DSM-IV (SCID-I), non-patient version, was used to assess psychiatric disorders. After subjects had responded for the Structured Clinical Interview, their bloods were extracted, and then they wrote the answer on the self-administered tests that assesses SRI and BPI. And IQ test for each subject was performed in the different day from the SRI and BPI tests. The exclusion criteria consisted of a history of psychosis, bipolar disorder, major depressive disorder, substance abuse or dependence, significant head injury, seizure disorder, and/or intellectual disability. This study was approved by the Institutional Review Board of Seoul National University Hospital and informed consent was obtained from all participants.

### Modified Form of the Stress Response Inventory (SRI-MF) Assessment

The present study employed a modified form of the Stress Response Inventory (SRI-MF) [26] that were derived from the original SRI questionnaire [27]. Each question in 22 questions was scored on a Likert-type scale that ranged from “not at all” (0), “somewhat” (1), “moderately” (2), “very much” (3), to “absolutely” (4). The 22 questions were categorized into three simplified stress factors: somatization, depression, and anger. Test–retest reliability of the SRI-MF was significantly high, ranging between 0.67 and 0.71 and Cronbach’s alpha was also high [26]. For the present study, the somatization subscale consisted of 9 items ( $\alpha=0.835$ ),

the depression subscale consisted of 8 items ( $\alpha=0.897$ ), and the anger subscale consisted of 5 items ( $\alpha=0.678$ ).

### Intelligence Quotient (IQ) Assessment

The present study used an abbreviated form of the Korean version of the Wechsler Adult Intelligence Scale [28]; this measure consisted of the vocabulary, arithmetic, block design, and picture arrangement subtests to estimate the full-scale IQ [29]. The abbreviated form was employed to decrease cognitive fatigue and improve cooperativeness. In addition to the above four scales, the digit span test was also administered to measure verbal working memory.

### Catecholamine Measurements

Plasma catecholamine concentrations were determined using high-performance liquid chromatography (HPLC) with a plasma catecholamine analysis system (Chromsystem). The mobile phase was prepared according to the specifications of the manufacturer, mixtures of NE, E, and DA at predetermined concentrations were used as external standards, and dihydroxybenzylamine was used as the internal standard. A CLC-300 dosing pump with a flow rate of 1.1 ml/min was connected to a reverse-phase catecholamine C-80 (code no. 5100/K) column. A CLC-100 electrochemical detector was used and its signal was registered and integrated by the Chromsystem Geminix registry and the calculation terminal.

### Brain Preference Indicator (BPI) Assessment

The BPI is a self-administered test that assesses hemispheric dominance; it consists of items that were normalized based on data obtained from electroencephalography (EEG) tests evaluating dominance that were performed at the Biofeedback Institute of Denver [30]. In its final form, the self-administered version has been completed by more than 500 people in the so-called Wonder seminars and the results are correlated with comparable laboratory tests [30]. In this test, subjects select the item that most closely represents their attitude or behavior. For the present study, questions with multiple-choice answers were deleted and Question 3 was eliminated; as a result, the final self-administered test consisted of 32 questions. The answer to each question was assigned a score and the sum of the average scores for all items ranged from 1 to 9; average scores of 1 or 9 indicated high lateralization. For this study, left-brain-dominant ( $<5$ ) and right-brain dominant ( $>5$ ) subjects were categorized based on the average score of 5.

### Data Analysis

Student's t-tests were conducted to analyze differences between two groups and Pearson's correlation coefficients were performed to analyze relationships between variables. P-values  $<0.05$  were considered to indicate statistical significance.

## Results

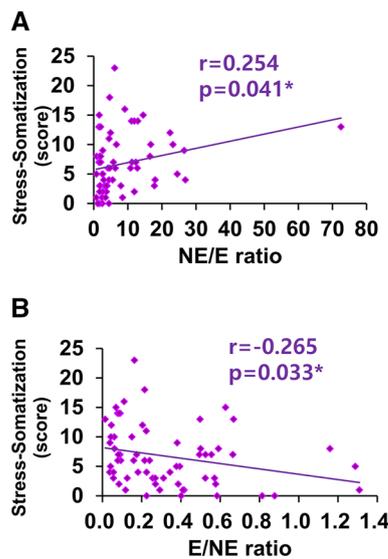
### Study Participants

Table 1 summarizes the demographic characteristics of the study subjects as well as their stress, IQ, BPI, and catecholamine levels.

**Table 1** Demographic characteristics and the levels of stress, IQ, BPI and catecholamins of the participants

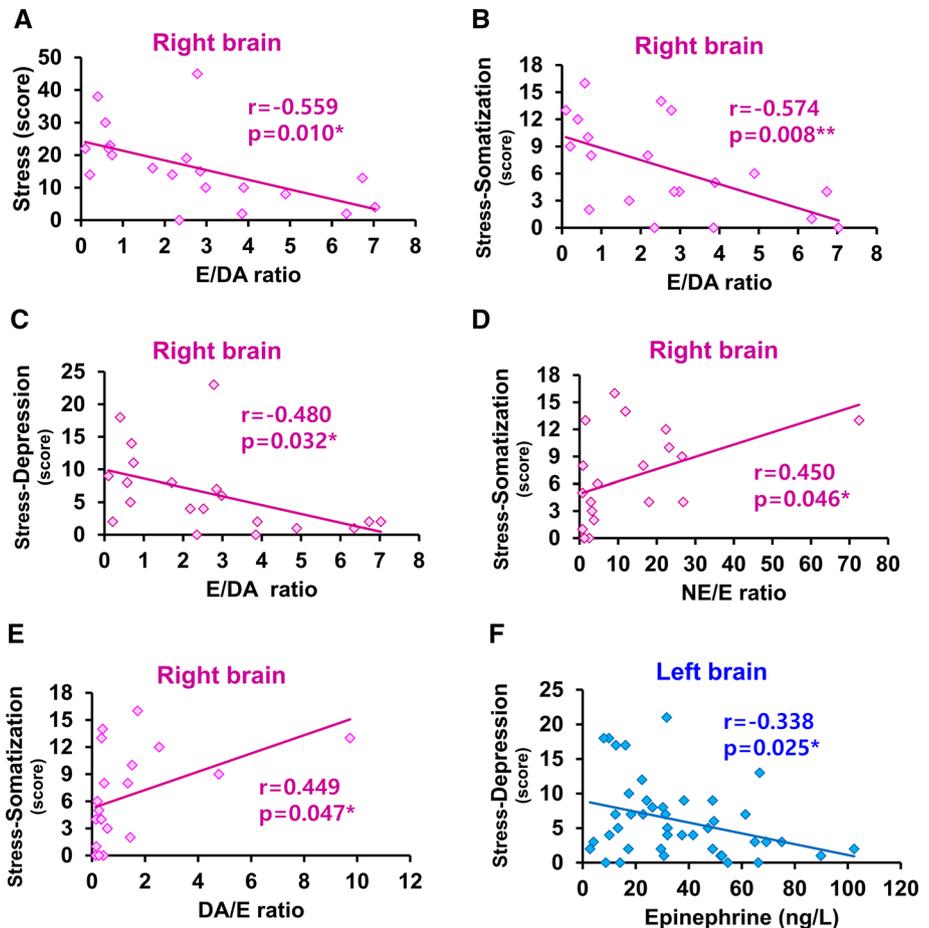
	Healthy controls (N = 70)	
	N	
	Male/female	39/31
	Mean	SD
Age	25.68 (range from 19 to 37)	3.89
Education (years)	14.47	1.41
SRI	16.75	12.23
Somatization	6.71	5.07
Depression	6.43	6.01
Anger	3.62	3.15
IQ	114.13	11.22
Vocabulary IQ	12.97	1.63
Digit span IQ	12.83	2.23
Picture arrange IQ	12.39	1.82
Block design IQ	13.64	2.48
Arithmetic IQ	12.79	2.63
BPI	4.68	0.79
Dopamine (ng/L)	15.41	13.19
Norepinephrine (ng/L)	135.96	87.70
Epinephrine (ng/L)	34.50	23.83
DA/NE ratio	0.15	0.15
DA/E ratio	0.87	1.41
NE/DA ratio	56.67	289.03
NE/E ratio	7.82	10.34
E/DA ratio	8.65	25.69
E/NE ratio	0.33	0.29

SRI stress response inventory, IQ intelligence quotient, BPI brain preference indicator



**Fig. 1** Correlations between catecholamine ratios and somatization of stress **a**, **b**  $n=65$

**Fig. 2** Correlations between catecholamine ratios and stress according to right or left hemispheric dominance **a–e**  $n=22$ , **f**  $n=44$

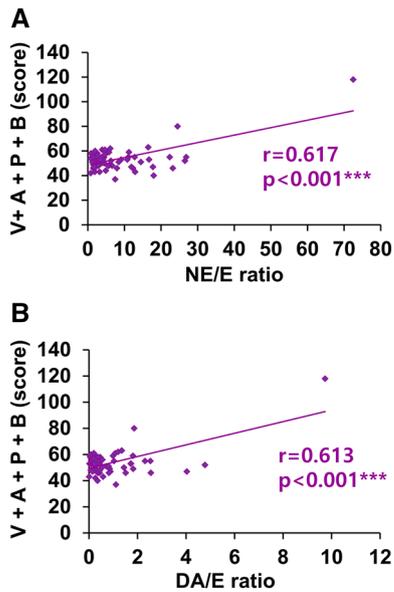


**Correlations Between Catecholamines and Stress**

The NE/E ratio was positively correlated with the somatization of stress ( $r=0.254, p=0.041$ ) and the E/NE ratio was negatively correlated with the somatization of stress ( $r=-0.265, p=0.033$ ) in the total number of subjects (Fig. 1). In the right-brain-dominant group, a E/DA ratio was negatively correlated with levels of stress ( $r=-0.559, p=0.010$ ), somatization ( $r=-0.574, p=0.008$ ), and depression ( $r=-0.480, p=0.032$ ; Fig. 2a–c). Additionally, high NE/E ( $r=0.450, p=0.046$ ) and DA/E ( $r=0.449, p=0.047$ ) ratios were associated with high levels of somatization in the right-brain-dominant group (Fig. 2d, e). On the other hand, E levels were negatively correlated with levels of depression ( $r=-0.338, p=0.025$ ) in the left-brain-dominant group (Fig. 2f).

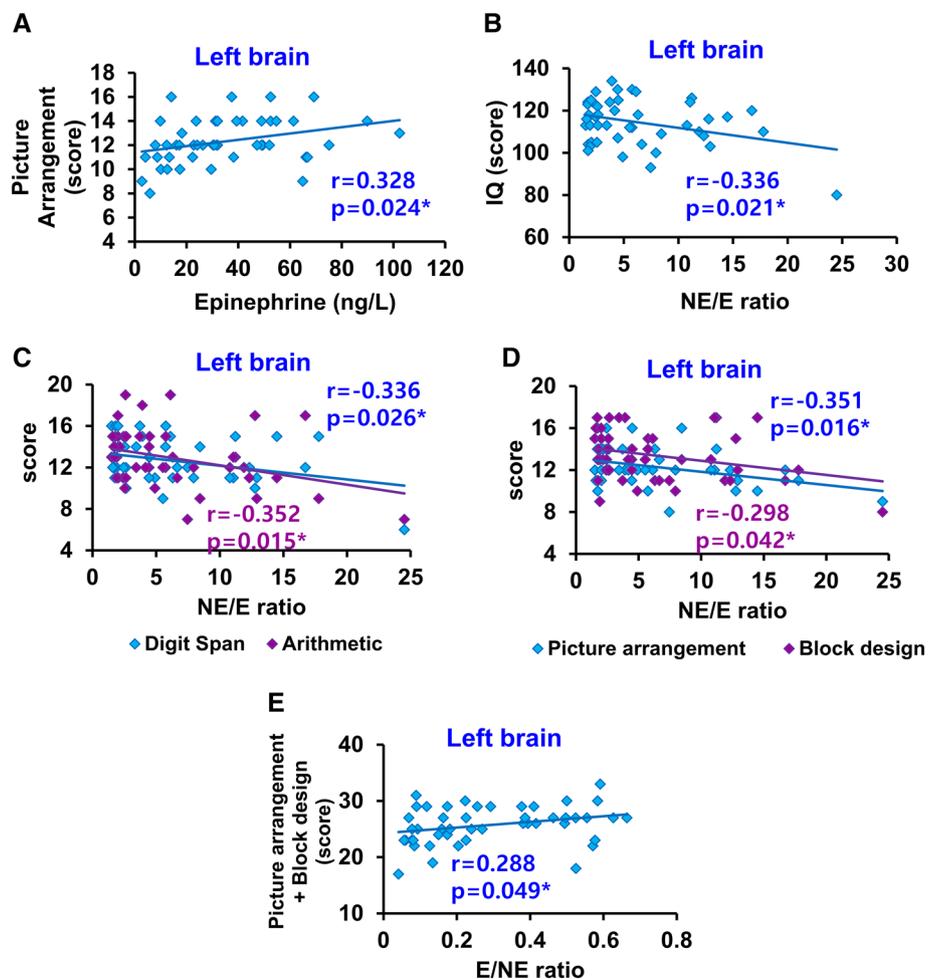
**Correlations Between Catecholamines and IQ**

The NE/E ( $r=0.617, p<0.001$ ) and DA/E ( $r=0.613, p<0.001$ ) ratios were positively correlated with the sum of

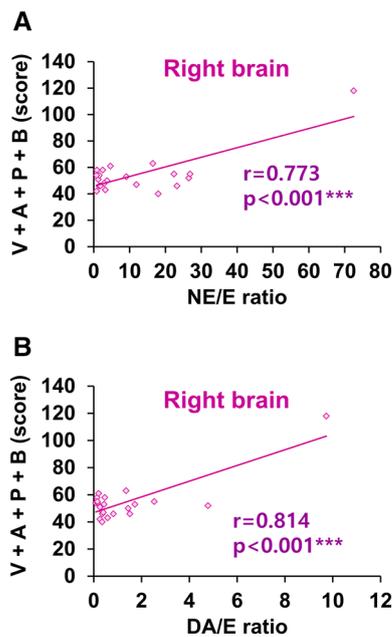


**Fig. 3** Correlations between catecholamine ratios and intelligence in total subjects. **a**  $n=70$ , **b**  $n=69$ . *V* vocabulary IQ, *A* arithmetic IQ, *P* picture arrangement IQ, *B* block design IQ

**Fig. 4** Correlations between catecholamine ratios and intelligence in left hemispheric dominance subjects **a–e**  $n=47$ . *IQ* intelligence quotient



the vocabulary, arithmetic, picture arrangement, and block design IQ subtests in the total number of subjects (Fig. 3). In the left-brain-dominant group, there were positive correlations between E and picture arrangement ( $r=0.328$ ,  $p=0.024$ ; Fig. 4a) and between E/NE ratio and picture arrangement and picture block ( $r=0.288$ ,  $p=0.049$ ; Fig. 4e). In the left-brain-dominant group, a NE/E ratio was negatively correlated with a full-scale IQ ( $r=-0.336$ ,  $p=0.021$ ; Fig. 4b) and scores on the digit span ( $r=-0.336$ ,  $p=0.026$ ) and arithmetic ( $r=-0.352$ ,  $p=0.015$ ) intelligence tests (Fig. 4c). Additionally, a NE/E ratio was negatively associated with scores on picture arrangement ( $r=-0.351$ ,  $p=0.016$ ) and block design ( $r=-0.298$ ,  $p=0.042$ ) in the left-brain-dominant group (Fig. 4d). On the other hand, the right-brain-dominant group exhibited positive correlations between the NE/E ( $r=0.773$ ,  $p<0.001$ ) and DA/E ( $r=0.814$ ,  $p<0.001$ ) ratios and the sum of the vocabulary, arithmetic, picture arrangement, and block design IQ subtests (Fig. 5).



**Fig. 5** Correlations between catecholamine ratios and intelligence in right hemispheric dominance subjects **a**, **b**  $n=22$ . *V* vocabulary IQ, *A* arithmetic IQ, *P* picture arrangement IQ, *B* block design IQ

## Discussion

The present study investigated associations between catecholamines and stress, and between catecholamines and IQ, in 70 healthy subjects. There was a positive correlation between the NE/E ratio and the somatization of stress but a negative correlation between the E/NE ratio and the somatization of stress in the total number of subjects. There were also positive correlations between the NE/E and DA/E ratios, and the sum of the vocabulary, arithmetic, picture arrangement, and block design IQ subtests in the total number of subjects. Furthermore, there were different associations of catecholamines with stress and IQ according to right and left hemispheric dominance. The positive correlation between the NE/E ratio and the somatization of stress implies that increased NE levels may affect the somatization of stress. It is well known that NE levels increase during conditions of stress or danger, which is the so-called fight-or-flight response [31]. Similarly, the present study found that a high NE/E ratio was associated with high levels of somatization of stress. Somatization is associated with a tendency to experience and communicate somatic distress in response to psychosocial stress [32]. On the other hand, the fact that E levels in the cerebrospinal fluid are reduced during somatizing depression [33] supports the present result that a low E/NE ratio was correlated with the high somatization of stress. Previous studies have shown that plasma NE levels are positively correlated with anxiety, and plasma

E levels are negatively correlated with an anxiety scale in pheochromocytoma-negative patients [34].

On the other hand, different relationships between catecholamine levels and stress were observed according to right and left hemispheric dominance. In the right-brain-dominant group, the associations of the NE/E and E/DA ratios with the somatization of stress were similar to those in the total number of subjects, and their correlation coefficients were higher than those of the total subjects. This suggests that right-brain-dominant subjects were more sensitive to the fight-or-flight response, showing the close relationships between NE/E, DA/E and E/DA ratios and the somatization of stress. Rat studies have demonstrated a hemispheric asymmetry such that the right PFC is normally dominant during the activation of stress-related systems while the left PFC may play a role in countering this activation via interhemispheric inhibition [23]. Additionally, the right cerebral hemisphere is dominant during the sympathetic activity associated with cardiac autonomic control [35]. In the present study, a high DA/E ratio was correlated with high levels of the somatization of stress in the right-brain-dominant group. DA plays a key role in the response to stress and is involved in many psychiatric disorders [9]. Moreover, DA release increases in response to aversive stimuli [36] and mesocorticolimbic DA levels increase during both acute and repeated social defeat stress [37]. Because dopaminergic activation in the right cortex is preferentially associated with uncontrollable stress [38], a higher DA/E ratio is acceptable during higher somatization of stress in right-brain-dominant subjects. On the other hand, in left-brain-dominant subjects, low E levels were associated with high levels of depression during stress. Previous reports have suggested that subjects with depression have more sensitive presynaptic alpha 2-adrenergic receptors and may have decreased sensitivity of the postsynaptic adrenergic receptors [39]. Accordingly, the E-innervated alpha 1-adrenergic system is impaired in depression and after stress [40].

The present study also demonstrated significant relationships between catecholamine levels and intelligence. It is well known that dopaminergic drugs enhance cognitive control [41] and that D1-mediated DA signaling in the PFC is predictive of general cognitive abilities, possibly due to its modulation of working memory [42]. Prefrontal cortical DA is associated with learning and memory [43] and DA acts as a powerful regulator of various cognitive brain functions [17]. Thus, a high DA ratio may contribute to high levels of intelligence on vocabulary, arithmetic, block design, and picture arrangement tests. On the other hand, the NE system, which includes both the sympathetic nervous system and the LC-centered system in the brain, is associated with stress and the HPA axis [4]. In the present study, there was a beneficial contribution of NE to the intelligence test subsets of vocabulary, arithmetic, block design, and picture

arrangement. These findings are supported by the fact that the neural noradrenergic system is thought to facilitate neuronal processes that promote behavioral activation, alertness, and attention as well as the modulation of cognitive function in the medial PFC [44]. Furthermore, the relationships between catecholamines and IQ revealed an effect of hemispheric asymmetry, i.e., left-brain-dominant subjects exhibited a beneficial relationship between E and the block design and picture arrangement IQ tests. In contrast, the NE/E ratio had a negative effect on intelligence in left-brain-dominant subjects, which probably resulted from the negative effects of stress via the HPA axis and NE system [4]. The DA/E and NE/E ratios had beneficial effects on the vocabulary, arithmetic, block design, and picture arrangement tests in right-brain-dominant subjects. However, the manner in which hemispheric dominance influences the relationships between catecholamines and IQ remains unclear. Continuous theta burst stimulation (cTBS) influences activity in the dorsolateral PFC (DLPFC) and indirectly interferes with task-induced striatal DA release [45]. Furthermore, cTBS applied to the left DLPFC interferes with the task-induced striatal DA release while cTBS applied to the right DLPFC does not affect Montreal Card Sorting Task (MCST)-induced DA release [46]. Subthreshold cTBS in the frontal cortex produces long-lasting inhibition in the underlying cortices [47]. Because the right PFC is normally dominant during the activation of stress-related systems, whereas the left PFC may play a role in countering this activation via inter-hemispheric inhibition [23], the specific inhibition of the left hemisphere may inhibit DA release. In fact, DA levels are higher in the right neocortex than the left neocortex [48]. Thus, it is possible that DA may make a positive contribution to intelligence only in right-brain-dominant subjects. However, there was a positive relationship between high DA levels and the high somatization of stress in the right-brain-dominant group, which may be due to resistance to environmental stress [49]. In the left-brain-dominant group, high E levels were associated with high levels of intelligence in the block design and picture arrangement tests. Given that E plays a role in the augmentation of memory consolidation [50], it may be beneficial for intelligence. For example, children with low urinary E levels during a stressor exhibit poorer task performance, whereas those with higher urinary E levels demonstrate improved selective attention and less deterioration in sustained attention [51]. Because E contributed to the decrease of stress in depression in this study, it may have beneficial effects on the resistance to stress as well as intelligence in left-brain-dominant subjects.

There are several limitations in this study that should be noted, particularly concerning multiple correlations. It is possible that Bonferroni corrections or other statistical corrections will be necessary to control for the false discovery rate. However, these approaches are not always needed

because reducing type I errors for null associations increases type II errors for associations that are not null [52, 53]. It is also possible that important findings will be missed when corrections for multiple correlations are used and, thus, a rather liberal threshold for significance was used in the present correlation analyses. Catecholamine levels in plasma may not reflect exact brain levels, even though there are evidences that peripheral levels of NE and DA may represent central catecholamine levels [54, 55].

In conclusion, the present study found a positive correlation between the NE/E ratio and the somatization of stress but a negative correlation between the E/NE ratio and the somatization of stress in the total number of subjects. Additionally, the NE/E and DA/E ratios had beneficial effects on the sum of the vocabulary, arithmetic, picture arrangement, and block design IQ subtests in the total number of subjects. Thus, in the present study, catecholamine levels were associated with stress and IQ, which suggests that stress, catecholamine levels and cognitive intelligence may be closely connected with one another in the brain. Additionally, relationships between these catecholamines and stress or IQ differed depending on right or left hemispheric dominance, supporting there is hemispheric asymmetry in their interactions between catecholamines and stress or cognitive intelligence.

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## Compliance with Ethical Standards

**Competing Interests** The authors declare no competing interests.

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