Sex differences in the relationship between cortisol levels and the Empathy and Systemizing Quotients in humans

Yoshihisa Nakayama [1], Taiki Takahashi [2], Akio Wakabayashi [3], Hidemi Oono [4] & Mark H. B. Radford [5]

1. Brain Science Institute, Graduate School of Engineering, Tamagawa University, Japan
2. Department of Cognitive and Behavioral Science, Graduate School of Arts and Sciences, The University of Tokyo, Japan
3. Department of Psychology, Faculty of Letters, Chiba University, Japan
4. Department of Biological Psychiatry, Tohoku University School of Medicine, Japan
5. Symbiosis Group Limited, Australia

Correspondence to: Taiki Takahashi,
Department of Cognitive and Behavioral Science,
Graduate School of Arts and Sciences, The University of Tokyo,
3-8-1, Komaba, Meguro-ku, Tokyo, 153-8902, Japan
EMAIL: taikitakahashi@gmail.com

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Abstract

OBJECTIVE: Little is known regarding the relationship between cortisol (a stress hormone) levels and psychological cognitive styles. Baron-Cohen proposed two fundamental cognitive styles, which are measured by the Empathy Quotient (EQ) and the Systemizng Quotient (SQ). Previous studies have examined the influences of prenatal testosterone exposure on EQ and SQ scores. This study aimed to examine the relationships between morning cortisol levels and EQ and SQ scores, and the 'brain types' which were determined by two quotients in both sexes. These relationships are potentially important in the developmental psychopathology of autism and neuroeconomics of empathy.
METHODS: We assessed morning cortisol levels with LC/MS (liquid chromatography-mass spectrometry) and ESQ in healthy male and female university students.
CONCLUSIONS: Results indicate clear sex differences between brain types: i.e. E-type males and S-type females (participants with atypical cognitive styles) have significantly higher cortisol levels than S-type males and E-type females (participants with typical cognitive styles). Implications for the role of sex in social adaptation of autistic patients are discussed.

ORIGINAL ARTICLE

INTRODUCTION

Recently it has been suggested that 'empathizing' and 'systemizing' are dimensions of 'essential difference' in the mind processes between males and females, although the underlying neuroendocrinological mechanisms are still unknown. Empathizing is described as being an important way in which we understand and predict our social world. Systemizing, on the other hand, is described as being an important way in which we understand and predict the law-governed inanimate universe

[1]. Systemizing is a process or drive, which allows us to analyze or construct systems, such as technical systems, natural systems, abstract systems, social systems (e.g. a political election, a legal system), organisable systems, and motoric systems [1]. On the other hand, empathizing is a psychological process or drive, which allows us to recognize another person's emotions and thoughts [1]. Empathizing is a broader concept than that often referred to as the 'theory of mind' (representing another person's mental state, intention, thought), which includes attributing one's own emotions or mental attitudes to others, nature, or art work (i.e. indicated by the word 'empathy' or 'sympathy'). Further, the nascent field of neuroeconomics has also started to study neural and hormonal correlates of empathy [2].

The Empathy Quotient (EQ) and the Systemizing Quotient (SQ) used in this study, were constructed to measure the degree of empathizing and systemizing in individuals and to test the E–S theory [3,4]. Both the EQ and SQ comprise 40 questions assessing empathizing or systemizing respectively. Using objective measures such as these, evidence is emerging that males are tend to score higher on systemizing and females score higher on empathizing [3].

According to the E–S theory, individuals who are higher on an empathizing style have a Type E (Empathizing) brain. Individuals who are higher on a systemizing style have a Type S (Systemizing) brain. Individuals in whom empathizing and systemizing are equally balanced have a Type B (Balanced) brain. Individuals with Asperger syndrome (AS) or high functioning autism (HFA) fit the profile of either average or even hyper-systemizing, with below-average empathizing. This brain type is described as an 'extreme Type S' [3].

In previous studies, we have shown that males scored higher than females on the SQ, and females scored higher than males on the EQ, irrespective of cultural differences [5]. Moreover, on average, more males than females have a Type S brain, and more females than males have a Type E [1,5,6,7]. Neuroeconomic studies also demonstrated, by utilizing functional magnetic resonance imaging (fMRI), that female brains show stronger empathic responses to others' pain than male brains, even in economic transactions and strategic social interactions [2].

Baron-Cohen and colleagues' extreme male brain hypothesis states that autism is associated with high SQ and low EQ, resulting in poor social skills and relatively potent ability to understand technical systems [1]. Studies have shown that the Autism-Spectrum Quotient (AQ) is positively related with a high SQ- and low EQ- (exaggerated male type) cognitive style [3]. The clinical finding that most autistic patients are males also supports the hypothesis. These results suggest that investigating neuroendocrinological sex differences in relation to EQ/SQ is important for a better understanding of the neuro-cognitive basis of autism.

In relation to the neuroendocrinological mechanism of autistic tendency (i.e. high SQ and low EQ), Auyeung et al. [8] suggested that fetal testosterone levels are associated with high SQ and low EQ in children. However little is known regarding the roles of EQ and SQ in modulating stress hormone (cortisol) levels. This point is important for elucidating the sex differences in social adaptation of patients with autism. It is important to reiterate here that typical males have an S-type (high SQ and low EQ) cognitive style, while typical females have an E-type (low SQ and high EQ) cognitive style.

Cortisol is known as a stress hormone, which is secreted via stress-induced amygdala-HPA (hypothalamic-pituitary-adrenal) activation, and modulates various types of neural activities [9]. Baseline and acutely elevated cortisol levels are associated with cognitive functions, such as memories [10,11], and attention [12]. Notably, morning cortisol levels are strongly correlated with participants' (trait) negative affect [13]. We have previously shown that interpersonal trust is negatively associated with social stress-induced cortisol elevation [14].

Several studies reported higher ACTH (adrenocorticotropic hormone) levels in individuals with autism/Asperger syndrome, but whether autistic patients have higher cortisol levels than normal control participants is still controversial [15,16]. This problematic situation is due to previous studies' lack of attention to sex differences in cognitive brain types (i.e. EQ/SQ). To our knowledge, no study to date has examined the role of sex in the relationship between autistic tendency in terms of EQ/SQ and stress hormone levels. Taken together, examining the relationship between a morning cortisol level (an indicator of participates' chronic, long-term stress levels, rather than short-term, state-dependent stress levels) and cognitive styles (i.e. EQ/SQ) is important to understanding sex differences in social adaptation of patients with autistic tendency. In an initial attempt to understand this relationship, we examine the relationships between morning cortisol levels and EQ/SQ scores in healthy male and female university students.

METHODS

Participants

A total of 128 (63 female; 65 male) healthy university students aged between 18 and 25 years participated in the present study. Participants with neuropsychiatric or neuroendocrine diseases were not included in the study.

Assessment of morning cortisol levels and cognitive styles

Saliva samples were collected from each participant in the morning of the experiment day (15–30 min after awakening). Saliva was collected from the participants using Salivette (Sarstedt, Rommelsdorf, Germany) collection devices. The saliva samples were stored at −20 °C until a biochemical analysis was conducted. Before assaying the saliva samples for cortisol, they were thawed and centrifuged, which results in low viscosity saliva. Cortisol levels in the saliva samples were assessed by Teikoku

Hormone Medical Co. Ltd. which has significant experience in various hormone assays, by utilizing LC/MS (liquid chromatography/mass spectroscopy) method [17], which can more precisely measure hormone levels than conventional radioimmunoassay (RIA). Staff at the company did not know the nature of the present study. On the same day, participants answered both the EQ and SQ questionnaires.

The Empathy Quotient (EQ) and Systemizing Quotient (SQ)

The original versions of the EQ and SQ are self-administered and force-choice formats. Each of them consists 60 items (40 items of measuring empathy/systemizing, 20 items of filler). In the present study, we used the short versions of the EQ (EQ-short) and the SQ (SQ-short), which were highly correlated with the original EQ and SQ, respectively [18]. EQ-short has 22 items (six of them are reversal items) are and SQ-short has 25 items (thirteen of them are reversal items). Participants have to choose the option for each question from "strongly agree", "slightly agree", "slightly disagree", and "strongly disagree".

Statistical analysis

EQ and SQ scores were calculated for each participant. Participants were then classified into three 'brain types': S-type (high systemizing and low empathizing), E-type (low systemizing and high empathizing), and B-type (a balanced cognitive style), according to criteria previously developed [18].

RESULTS

The characteristics of morning cortisol levels and EQ/SQ of the participants are presented in Table 1. Participants' averaged morning cortisol levels were similar to values reported in previous studies employing LC/MS [19]. As noted above, participants' brain type was determined by their EQ and SQ scores. We found 56 participants were non-B type (i.e. did not have a balanced cognitive style). Of this group we found eight E-type males, 16 S-type males, 23 E-type females, and nine S-type females. The observed sex difference in brain types is consistent with previous finding that males tend to be S-type, while females tend to be E-type. We found no main effects (sex nor brain type differences) for morning cortisol levels (Sex: $p=0.624>0.05$; Type: $p=0.662>0.05$). In order to further examine the role of sex in the relationship between morning cortisol levels and brain type, we analyzed the interaction between brain type and sex. We observed a significant interaction between sex and cognitive brain styles ($p=0.026<0.05$, Figure 1). Namely, male E-type and female S-type participants had significantly higher morning cortisol levels in comparison to male S-type and female E-type participants.

DISCUSSION

This study is the first to report that male E-type and female S-type participants have higher cortisol levels in the morning (waking cortisol levels) than male S-type and female E-type participants. This 'atypical' finding could have interesting clinical implications, as it has also been reported that elevated waking cortisol levels are associated with depression and neuroticism [20,21]. It is again to be noted that the extreme male brain theory of autism states that essential characteristics of autistic tendency is an extremely male-type cognitive style (i.e., a hyper-systemizing and impaired empathizing tendency), indicating that S-type participants may be more "autistic" than E-type participants [1]. Taken together, S-type females (i.e., females with high autistic tendency) may be more susceptible to mood disorders such as depression than males with high autistic tendency. In contrast, E-type males (i.e., atypically "less autistic" males) may be more susceptible to mood disorders than E-type females (i.e., typically "less autistic" females). Regarding sex differences in stress-induced cortisol elevation, a previous study [22] reported that females are more responsive to social rejection; while males are more responsive to achievement challenge. Considering that avoiding social

Table 1. Means (SDs) of the participants' morning cortisol levels and EQ/SQ scoring.

	Female (N=63)	Male (N=65)
Morning cortisol levels (ng/mL)	3.38 (2.09)	3.21 (1.81)
EQ	34.38 (10.81)	33.17 (10.23)
SQ	18.90 (10.19)	25.20 (10.56)

We did not observe main effect of sex on morning cortisol levels.

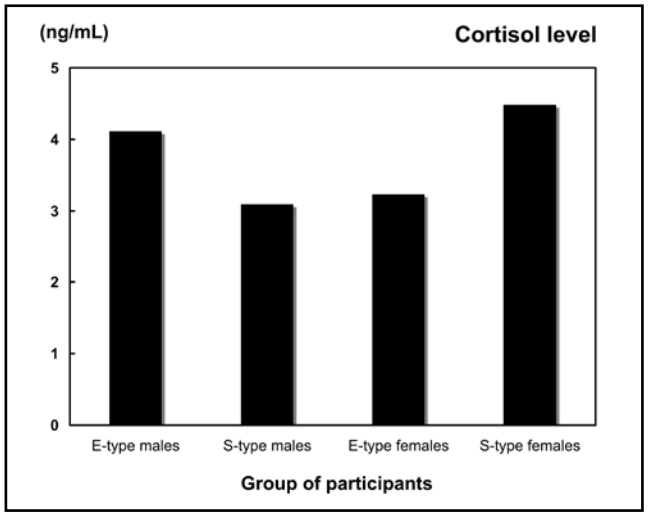

Figure 1. Morning cortisol level of each Baron-Cohen's brain type in males and females. The vertical axis indicates morning cortisol levels in the saliva (ng/mL). E-type males and S-type females (atypical Brain type-subjects) had significantly higher cortisol levels than S-type males and E-type females (typical Brain type-subjects).

rejection requires potent social skills and achievement challenge may require (non-social) systemizing abilities, this finding is in line with our present finding that high autistic tendency (S-type cognitive style) is psychoneuroendocrinologically more detrimental to females than males. On the basis of this finding it is important that future studies examining the difference in cortisol and ACTH levels between control and individuals with autism/Asperger syndrome should pay attention to sex differences.

It has been suggested that the relationship between E–S brain types and sex could have biological and genetic origins. Specifically, systemizing ability may have enhanced male adaptation in evolutionary processes as a law-detector and a change-predicting device, while empathy may have enhanced female adaptation [23]. Our results further extend this understanding into the social adaptation domains, suggesting that autistic tendency may be a type of over-adaptive systemizing and impaired empathizing function, which is consistent with the extreme male brain theory of autism.

Limitation and future directions

In this study we did not assess participants' testosterone levels. Developmental psychopathological studies have demonstrated that excessive prenatal testosterone exposure is associated with S-type cognitive style [8]. Furthermore, recent neuroendocrinolgocial studies have shown that testosterone is converted into estradiol (a female hormone) in the brain regions such as the hippocampus [24]. Both the relationship between testosterone and estradiol, and E–S brain types should be examined in future studies. Concerning neuroeconomics of empathy [2], because little attention has been paid to E- and S- brain types in examining sex differences in empathic brain responses to others' pain and monetary loss, future studies should consider participants' brain types (E- or S- type), in addition to sex.

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REFERENCES

1 Baron-Cohen S. The extreme male brain theory of autism. Trends in Cognitive Sciences. 2002; **6**: 248–254.
2 Singer T and Fehr E. The neuroeconomics of mind reading and empathy. American Economic Review. 2005; **95**(2): 340–345.
3 Baron-Cohen S, Richler J, Bisarya D, Gurunathan N, & Wheelwright S. The systemizing quotient: An investigation of adults with Asperger syndrome or high-functioning autism, and normal sex differences. Philosophical Transactions of the Royal Society of London. 2003; **358**: 361–74.
4 Baron-Cohen S, & Wheelwright S. The empathy quotient: An investigation of adults with Asperger syndrome or high functioning autism, and normal sex differences. Journal of Autism and Developmental Disorders. 2004; **34**: 163–75.
5 Wakabayashi A, Baron-Cohen S, Uchiyama T, Yoshida Y, Kuroda M, & Wheelwright S. Empathizing and systemizing in adults with and without autism spectrum conditions: Cross-cultural stability. Journal of Autism and Developmental Disorders. 2006; **37**(3): 491–500.
6 Goldenfeld N, Wheelwright S, & Baron-Cohen S. Empathizing and systemizing in males, females and autism. International Journal of Clinical Neuropsychiatry. 2005; **2**: 338–345.
7 Wheelwright S, Baron-Cohen S, Goldenfeld N, Delaney J, Fine D, Smith R, Weil L, & Wakabayashi A. Predicting autism spectrum quotient (AQ) from the systemizing quotient-revised (SQ-R) and empathy quotient (EQ). Brain Research. 2006; **1079**: 47–56.
8 Auyeung B, Baron-Cohen S, Chapman E, Knickmeyer R, Taylor K, & Hackett G. Foetal testosterone and the child systemizing quotient. European Journal of Endocrinology. 2006; **155**: S123–S130.
9 Takahashi T, Kimoto T, Tanabe N, Hattori TA, Yasumatsu N, & Kawato S. Corticosterone acutely prolonged N-methyl-d-aspartate receptor-mediated Ca2+ elevation in cultured rat hippocampal neurons. Journal of Neurochemistry. 2002; **83**: 1441–1451.
10 Nakayama Y, Takahashi T, & Radford MHB. Cortisol levels and prospective and retrospective memory in humans. Neuro Endocrinol Lett. 2005; **26**: 599–602.
11 Takahashi T, Ikeda K, Ishikawa M, Tsukasaki T, Nakama D, Tanida S, & Kameda T. Social stress-induced cortisol elevation acutely impairs social memory in humans. Neuroscience Letters 2004; **10**: 125–130.
12 van Honk J, Tuiten A, van den Hout M, Koppeschaar H, Thijssen J, de Haan E, & Verbaten R. Baseline salivary cortisol levels and preconscious selective attention for threat. A pilot study. Psychoneu roendocrinology. 1998; **23**: 741–747.
13 Polk DE, Cohen S, Doyle WJ, Skoner DP, Kirschbaum C. State and trait affect as predictors of salivary cortisol in healthy adults. Psy choneuroendocrinology. 2005; **30**(3): 261–272.
14 Takahashi T, Ikeda K, Ishikawa M, Kitamura N, Tsukasaki T, Nakama D, Kameda T. Interpersonal trust and social stress-induced cortisol elevation. Neuroreport. 2005; **16**: 197–199.
15 Curin JM, Terzic J, Petkovic ZB, Zekan L, Terzic IM, Susnjara IM. Lower cortisol and higher ACTH levels in individuals with autism. J Autism Dev Disord. 2003; **33**: 443–448.
16 Tani P, Lindberg N, Matto V, Appelberg B, Nieminen-von Wendt T, von Wendt L, Porkka-Heiskanen T. Higher plasma ACTH levels in adults with Asperger syndrome. J Psychosom Res. 2005; **58**: 533–536.
17 Takahashi T, Sakaguchi K, Oki M, Homma S, Hasegawa T. Testosterone levels and discounting delayed monetary gains and losses in male humans. Neuro Endocrinol Lett. 2006 Aug; **27**(4): 439–444.
18 Wakabayashi et al. Development of short forms of the Empathy Quotient (EQ-Short) and the Systemizing Quotient (SQ-Short). Personality and Individual Differences. 2006; **41**: 929–940.
19 Kataoka H, Matsuura E, Mitani K. Determination of cortisol in human saliva by automated in-tube solid-phase microextraction coupled with liquid chromatography-mass spectrometry. J Pharm Biomed Anal. 2007; **44**: 160–165.
20 Bhagwagar Z, Hafizi S, Cowen PJ. Increased salivary cortisol after waking in depression. Psychopharmacology (Berl). 2005 Oct; **182**(1): 54–57.
21 Portella MJ, Harmer CJ, Flint J, Cowen P, Goodwin GM. Enhanced early morning salivary cortisol in neuroticism. Am J Psychiatry. 2005 Apr; **162**(4): 807–809.
22 Stroud LR, Salovey P, Epel ES. Sex differences in stress responses: social rejection versus achievement stress. Biol Psychiatry. 2002; **52**(4): 318–327
23 Baron-Cohen S. The hyper-systemizing, assortative mating theory of autism. Prog Neuropsychopharmacol Biol Psychiatry. 2006; **30**(5): 865–872.
24 Hojo Y, Hattori TA, Enami T, Furukawa A, Suzuki K, Ishii HT, Mukai H, Morrison JH, Janssen WG, Kominami S, Harada N, Kimoto T, Kawato S. Adult male rat hippocampus synthesizes estradiol from pregnenolone by cytochromes P45017alpha and P450 aromatase localized in neurons. Proc Natl Acad Sci U S A. 2004; **101**(3): 865–870.