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Plasma Cortisol Response to Asked Questions on Recent Events during Videogame Play in Individuals with Autism Spectrum Disorders

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Abstract One of the core symptoms of autism spectrum disorders (ASD) is the need for consistency, repetition, rituals, and rigid patterns of play. The need for sameness may be extended to include videogame play and interaction with others.Unfamiliar social interactions and disruption of repetitive patterns of interests and behavior may easily exacerbate anxiety-related stress in individuals with ASD. Whereas, videogame can induce distraction of stress response. We examined the effects of videogame play on cortisol social under the situations of asked questions on daily events plasma.We conducted astructuredinterview consisting of the declarative memory recallon daily events during videogame.Before the start of the interviews, each participant played a videogame as the default context. Two serial contexts followed in which participants were exposed to different social stimuli. Twotypes of stimulators such as an unfamiliar female and an unfamiliar male asked the participants questions on unpleasant daily events, respectively. Immediately after these interviews, the participants were permitted to resume the video game play.A blood specimen for plasma cortisol determination were conducted twice: once at the time of 28 days before and again 5 minutes after the interviews.There were no significant differences in plasma cortisol levels between before and after the interview questions in the 10 children with ASD and the 7 normal healthy controls. Disruption of videogame play, asked questions conducted by the unfamiliar adults, and memory retrieval for the unpleasant daily life events may be able to increase plasma cortisol levels. However, plasma cortisol levels in the 10 children with ASD were not significantly increase plasma cortisol response. Considering that video playing has been found toinduce distraction or decrease and no stress response, video game play candistract cortisol response to stressors.

Keywords: *autism spectrum disorders, video game play, memory retrieval, distress events, plasma cortisol levels*

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1. Introduction

Deficits in social relatedness and communication, and circumscribed interests and behaviors were characteristics of autism spectrum disorders (ASD) [1]. Particular, encompassing preoccupation with one or more stereotyped and restrictive patterns of interests is characteristic manifestation in individuals with ASD [1]. It is well known that the core features of ASD induce the need for consistency, repetition, rituals, predictability and rigid patterns of play and problem solving [2]. The constant changing nature of unfamiliar social interactions and social situations that require spontaneous intuitive adjustment may exacerbate socially related anxiety for these children with ASD [2]. Social unfamiliarity may therefore easily induce anxiety and stress in individuals with ASD [2].

There is accumulating evidence indicating that individuals with ASD have hypersensitive to psychosocial stress. To the extent to which the situation is perceived as stressful, one of the useful biological marker is salivary [2,3] or plasma [4,5].

In order to avoid stress associated with collection of blood samples, many previous studies measured cortisol in saliva. Twenty children with ASD aged 3 to 10 years showed significantly higher salivary cortisol response to blood draw stressor compared to age matched 28 children withoutASD [6]. To examine psychosocial stress such as public speaking task [7] or closely relationship between increased sensory sensitivity and variable cortisol secretion (Corbett et al, 2009) [8] was used in children with ASD. Moreover, in many previous studies examining the effect of self-reported social anxiety/stress in relation to peer interaction, salivary cortisol levels were used as a biological marker of stress [2,8,9]. For example, salivary cortisol levels were significantly increased ininteraction with unfamiliar peers in 33 children with ASD compared

to interaction with familiar peers [2]. The peer interaction paradigm resulted in significantly higher levels of salivary cortisol in 21 children with ASD aged 8 to 12 yearscompared to normal controls, suggesting that theASDchildren easily activate hypothalamic-pituitary-adrenal (HPA) responses in social situations [9]. Forty-five prepubescent male children with ASDaged 8 to 12 years maintained an elevated cortisol level in response to standardized social-evaluative performance task compared to children with typical development [10]. The children who exposed to the stressful condition showed pronounced increases ofsalivary cortisol [11]. While, ASD patients (mean age of 21.8±2.0 years)showed the dissociation between heart rate and cortisol responses due to a physiological dysfunction in ASD [7].Extrapolating from these findings, children with ASD may be easily stressed, and increase salivary cortisol levels by human interaction.

It has been well known that salivary cortisol and total plasma cortisol have been found to show a strong concordance of results [12]. Moreover, saliva is generally sampled by swabbing the mouth with a soft cotton roll, which reteins 135-450 µlof saliva after centrifugation [13]. These volumes can make a crucial difference between being abate to measurable a reliable cortisol concentration and having to throw away a valuable sample because of lack of sufficient material [13]. We thus used the plasma cortisol levels as a biomarker of stress response.

The majority of youths with ASD (64.2% of the 860 youth with ASD) aged 13 to 17 years spent most of their free time using non-social media (television, video games), while only 13.2% spent time on social media (email, internet chatting) [14]. Compared with other disability groups (speech/language impairments, learning disabilities, intellectual disabilities), rates of non-social media use were higher among the ASD group, and rates of social media use were lower [14]. Moreover, 202 children with ASD spent approximately 62.0 % subjects with ASD aged 8 to 18 years more time watching television and playing video games than in all non-screen activities combined. Compared with typically developing siblings, children with ASD spent more hours per day playing videogames (2.4 vs. 1.6 for boys, and 1.8 vs. 0.8 for girls) [14].

Some effects of video game are harmful (such as effects of violent videogames on aggression and the effect of screen time on poorer school performance), whereas others are beneficial (e.g., effects of action games on visual-spatial skills) [15]. Videogame effects are complex and would be better understood as multiple dimensions rather than a simplistic “good-bad” dichotomy [15]. Video game playdid not increase up-regulation of salivary serum [16] or salivary [17] cortisol levels. Moreover, casual videogame decreased physiological stress responses [18].Videogame play may thus not increase plasma or salivary cortisol levels, or decrease physiological stress responses.

As described above, one of the core symptoms of ASD is the need for consistency and repetition patterns of play. This need for sameness may be extended to include videogame play and interaction with others.Social interactions with unfamiliar adults, and disruption of repetitive patterns of interests and behavior may easily exacerbate anxiety-related stress in individuals with ASD. Whereas, videogame can induce distraction of such stress response. It is possible that different types of psychosocial stress such as interruption of videogame play, asked questionsmay be attenuated by videogame play andplasma cortisol levels individuals with ASD. The purpose of this study attempt to untangle this possibility.

2. Materials and Methods

2.1. Participants

This study included 10 individuals with ASD (8 male and 2 female) with age of 6-13 years (mean ± SD, 10.90 ± 4.04 years), and 7 normal healthy controls (3 male and 4 female)with age of 6-19 years (mean ± SD, 11.71 ± 4.11 years). The Statistical Manual of Mental Disorders-Fourth Edition (DSM-IV) [20] was employed for diagnoses. For diagnoses of ASD, the semi-structured clinical interview based on the Autism Diagnostic Interview Revised (ADI-R) [20] was also used. The agreement of two independent, experienced psychiatrists was required for a diagnosis. At screening, physical (resting blood pressure and heart rate) and clinical laboratory examinations (hematology, plasma chemistry including plasma cholesterol and tryglyceride) of the individuals were performed. Among the 10 children with ASD, 6 were recruited through a local advertisementof the Research Institute of Ashiya University at February 2009-October 2012. Other 4 children with ASD were recruited through local advertisementof the Research Institute of Ashiya University at November 2011.

2.2. Study Procedures

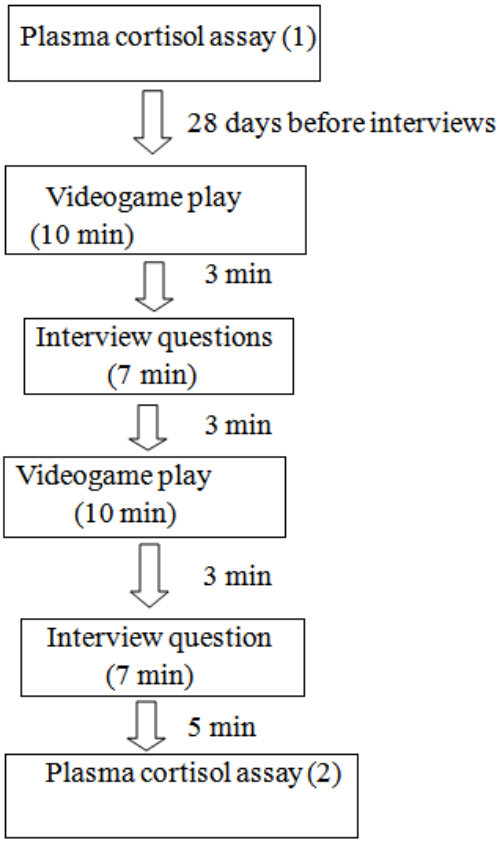

Figure 1. The experimental time sequence used to the stress response of individuals with ASD and normal controls

We conducted astructuredinterview consisting of the declarative memory recallduring video game for 40 minutes.Before the start of the interviews, each participant played a TV-based videogame as the default context. Two serial contexts followed in which participants were exposed to different social and emotional stimuli for 7 minutes each (a total of 14 minutes) during which time all individuals were ceased videogame play by oral request of two types of stimulators. Twotypes of the stimulators such as an unfamiliar female and an unfamiliar maleasked the participants questions on unpleasant daily events, respectively. For example, “What was your most pleasant experience recently?” As unpleasant one asked was; “What was your most unpleasant experience recently?” “Did you have a difficult time at school today?” Immediately after these interviews, the participants were permitted to resume the role-play videogame play (reference to Figure 1).

2.3. Measures

Clinical outcome evaluations were carried out at the baseline and 4, 8, 12 and 16 weeks after the intervention, using the Social Responsiveness Scale (SRS) [22] and ABC [22]. The SRS and ABC subscales were completed by the parent.

2.3.1. Social Responsiveness Scale (SRS)

The SRS is a 65-item quantitative measure of autistic social impairment completed by an informant who had regularly observed the subject in naturalistic social contexts over a period of at least 2 months. SRS scores are unrelated to age in the range from 7 years to 18 years and do not vary as a function of race, ethnicity, or the rater’s level of education [23].

2.3.2. Aberrant Behavior Checklist (ABC)

The ABC, which was originally developed to measure problem behaviors in developmentally disabled populations, is a good measure of associated with ASD and mental retardation, and has emerged as one of several important end points for assessing treatment effects in ASD psychopharmacologic and behavioral intervention trials in children and adolescents with intellectual disability [22] and also normal IQ levels [24]. The IQ scores are therefore needed in this study. The ABC includes five subscales: irritability, social withdrawal, stereotypy, hyperactivity and inappropriate speech in conjunction with a clearly established and validated factorial structure [22].

2.4. Cortisol Sampling and Assay Procedures

Following an overnight fast, a blood specimen for plasma cortisol determination were conducted twice: once at the time of 28 days before and again 5 minutes after the interviews. All blood samples were obtained at 13:00-15:00 PM in the seated position after at least 15 minutes of rest. Plasma, obtained within 5 minutes of collection by centrifuging whole blood, and the plasma was stored at -70°C until further analysis. Analysis was carried out by SRL, Inc, Tokyo, Japan.

Plasma cortisol levels were measured by radioimmunoassay (Amersham Pharmacia Biotech, TFB Co., Tokyo, Japan). The intra- and inter-assay coefficients of variation were 7 % or less and 9 % or less respectively (SRL, lnc, Tokyo, Japan).

3. Results

3.1. Descriptive Characteristics

There was no significant difference in age between the 10 individuals with ASD and the 7 normal healthy controls (U=30.50, p=0.67). The subscale of awareness, cognition, communication, motivation, and mannerisms of the SRS in the 10 children with ASD were significantly higher than the 7 normal controls ($p<0.05$). All of the 17 individuals have no abnormalities in physical and laboratory examinations. The subscale scores of irritability, hyperactivity and inappropriate speech were significantly higher than the 7 normal controls ($p<0.05$). The total scores of the SRS and ABC were 61.10±32.82 and 24.70± 19.97, respectively.Earlier studies have reported total SRS and ABC scores of 101.7±22.1 [25] and 85.6±27.3 [26], respectively, for children and adolescents with ASD.Our 10children with ASD were thus considered to have mild conditions. However, they have delayed social skills and/or extreme difficulties with organizational skills. They display behavior, interests, and activities that are restricted and repetitive patterns of behavior and activities. As a result, they found public school or work settings moredifficult than the normal developed peers (Table 1).

Table 1. Demographics of subjects

	Children with ASD (N=10)	Normal controls (N=7)	Mann-Whitney U-test	
			U	P
Mean age at study	10.90 (4.04)	11.71 (4.11)	31.50	0.74
SRS scores				
Awareness	8.20 (4.10)	2.71 (2.81)	16.50	0.014*
Cognition	12.60 (4.10)	2.71 (2.81)	7.0	0.005*
Communication	19.00 (12.02)	2.71 (3.45)	6.50	0.003*
Motivation	9.10 (6.77)	3.29 (3.68)	15.00	0.050
Mannerisms	9.90 (6.47)	1.14 (1.86)	8.00	0.007*
Total score	61.10 (32.82)	12.57 (13.02)	8.00	0.007*
ABC scores				
Irritability	6.40 (0.87)	0.14 (0.38)	8.50	0.007*
Social withdrawal	5.50 (5.42)	1.14 (2.27)	19.00	0.133
Stereotypy	1.70 (2.21)	0.29 (0.76)	18.50	0.109
Hyperactivity	9.90 (8.63)	1.14 (1.86)	9.0	0.010*
Inappropriate speech	2.40 (2.22)	0.26 (0.49)	14.50	0.043*
Total scores	24.70 (19.97)	3.14 (5.13)	10.00	0.014*

Data expressed as mean (SD). * P<0.05 compared between the children with ASD and normal controls.

3.2. Plasma Levels of Cortisol

There were no significant differences in plasma cortisol levels between the 10 children with ASD and the 7 normal controls at 28 days before the interviews, and at 5 minutes after the interviews. There were no significant difference in plasma cortisol levels between 28 days before and 5 minutes after of the in interviews in the 10 children with ASD, and also in the 7 normal controls (Table 2).

Table 2. Plasma levels of cortisol (ng/ml)

		Children with ASD (N=10)	Normal controls (N=7)	Mann-Whitney U-testa)	
				U	P
28 days Before		8.29 (4.91)	9.36 (7.05)	34.00	0.962
Five minutes after		7.90 (3.31)	7.46 (3.87)	33.50	0.887
Mann-Whitney U-testb)	U	49.50	23.50		
	P	0.971	0.902		

Data expressed as mean (SD). a)Data were compared between the children with ASD and normal controls. b) Data were compared between 28 days before and 5 minutes after the interview questions in the children with ASD and normal controls respectively.

4. Discussion

The constant changing nature of unfamiliar social interactions and social situations may exacerbate socially related stressin individuals with ASD [2]. The need for sameness may be extended further to include patterns of familiarity and interactions with others [2]. These considerations taken together, the 11 individuals with ASD may be easily stressed by interrupting video game play and communication with the novel adults.

Salivary cortisol levels were used as a biomarker for psychosocial stress response [2,3]. Method on saliva assay has drawbacks because of lack of sufficient material [13]. Salivary cortisol and total plasma cortisol have been found to show a strong concordance of results [12]. Drawing these consideration together, we examined the plasma cortisol levels as a biomarker of stress response to interview questions.

According to previous studies on elevated salivary cortisol response to psychosocial stress,twenty children with ASD aged between 3 to 10 years showed significantly higher salivary cortisol response to blood draw stressor compared to age matched 28 children without ASD, suggesting increased reactivity of the hypothalamic-pituitary axis (HPA) to novel stimuli in children with ASD [6]. The 10 children with ASD (mean age, 9.4 ± 1.4 years) showed a significantly elevated salivary cortisol response to psychosocial stress, consisting of public speaking task than the 12 normal healthy controls (mean age, 9.4 ± 1.5 years), indicating disturbed reactions in the 10 children with ASD [7]. Significant correlationswere found between salivary cortisol levels and self-reported distress ratings within both familiar and unfamiliar peers, indicating a more complex relationshipsuch as the role of anticipation in the stress response or acute coping differences in the children in each of the counterbalance conditions [2]. The peer interaction paradigm resulted in significantly higher levels of salivary cortisol in 21 children with ASD aged 8 to 12 yearscompared to 24 age-matched normal controls, suggestingactivation of hypothalamic-pituitary-adrenal (HPA) responses in social situations [9]. Their additional study revealed that ASD group consisting of 27 male individuals with ASD aged between 8 to 12 years maintained an elevated cortisol level compared to 32 children with typical development in response to standardized social-evaluative performance task [10]. A recent study measured cortisol levels in children with and without Autism: (1) at rest; (2) in a novel environment; and (3) in response to a blood draw stressor. A significantly higher serum cortisol response was found in the group of children with ASD [6]. These findings suggests increased reactivity of the hypothalamic-pituitary axis to novel stimuli in children with ASD[6].According to a previous study comparing cortisol, stress and sensory sensitivity in children with ASD aged between 6 to 12 years (mean age, 9.08 years), increased sensory sensitivity related to variable cortisol secretion, may be related to plausible developmental factors [8]. Extrapolating from these findings, children and also adults with ASD may be easily stressed by human interaction. Individuals with ASD showed hypersensitive to human interaction as measured by increases in salivary cortisol levels.

Although salivary cortisol levels are usually used as a biomarker of stress response in children with ASD to avoid stress associated with collection of blood samples, a lot of studies uses plasma cortisol response as a biomarker of psychosocial stress. For example, public speaking induced significantly increased before and up to 90 minutes after the stressor in 106 healthy adolescents aged 18 to 19 years [4]. The public speaking evoked significantly increased plasma cortisol levels in 79 healthy adolescents or young adults aged 18 to 27 years compared to a no demanding task in 30 age-matched subjects [27]. Drawing these strands together, the 10 individuals with ASD could have shown to increase cortisol response.

In this study, two types of stimulators such as an unfamiliar female and an unfamiliar male asked the questions at the time which they were ceased video game play. The structured interviews encompassed the memory retrieval of most unpleasant daily events in their personal relationship to their peers or teachers in their school. These settings included three kinds of stress such as interrupting game play, interaction with the novel adults, and retrieval of distressing memory. Considering that one of the insistent sameness and most consistent characteristic of ASD is the lack of understanding of social ability, and that personal interaction with unfamiliar adults may have been able to induce stress response in the 10 individuals with ASD.

In respect to the effects of memory retrieval on cortisol response, an inverted U-shaped dose-response relationship between salivary cortisol levels and recall performance was observed with moderate elevation of salivary cortisol resulting in the best recall performance [28]. Moreover, memory retrieval testing after the learning session was strongly associated with urine cortisol secretion[29] or salivary cortisol response [30]. Therefore, memory retrieval of the unpleasant daily events may have been induced increased plasma cortisol response.

Collectively, disrupting game playing, the asked questions conducted by the unfamiliar adults, and memory retrieval of the life events or daily happening may have induced HPA-related stress response, increasing plasma cortisol levels. However, plasma cortisol levels in the 10 children with ASD were not significantly increased in the above described test setting. Video game playing increased sympathetic tone, mental workload, and energy expenditure, however, did not suggest up-regulation of serum cortisol levels [16]. The violent and non-violent TV videogame did not induce significant differences in salivary cortisol levels before and after gaming [17]. Interestingly, casual videogame induced autonomic

nervous system relaxation or decreased physiological stress responses in electroencephalographic changes and hear rate variability [18]. The videogame successfully distracted patients during the dental procedure accompanied by an increase in physiologic arousal [31]. Drawing these strands together, the video game play may distract plasma cortisol response to stressful setting. Psychoendocrinological factors associated with flat responses of cortisol profile in the 10 children with ASD in this study are not clearly understand.

Three factors may be considered as follows: first, psychosocial stress induced by the above described possibly stressful situation (such as the disrupting videogame play, asked questions in relation to memory retrieval of unpleasant daily events, and communication with the novel persons) may be attenuated by videogame play. Second, considering previous finding that younger children with ASD show an enhanced willingness to approach others and seem to do so without apparent stress, and showed a lower cortisol response in setting which was provided behavioral structure to the free play by permitting key interactive sequences [32], the 10 individuals with ASD in this study may be willing to approach unfamiliar adults, and thus showed no changes of plasma cortisol response. Third, our interview questions may have less impact on plasma cortisol response.

The present findings might provide useful information on the distracted effects on physiological or psychological stress in social interaction in ASD. However, there is lack of data on plasma cortisol response to the same interviews without videogame play in this study. The effect of videogame play on distraction in stress reduction is needed in further studies.

In conclusion, plasma cortisol response to stressful situations such as the disrupting video game play, asked questions in relation to memory retrieval of unpleasant daily events, and communication with the novel persons may be attenuated by video game play.

Authors' Contributions

Kunio Yui wrote the article. Masako Ohnishi contributed to collection of clinical characteristics from subjects with autism spectrum disorders. All authors read and approved the final manuscript.

Conflict of Interest

The authors have declared that no conflict of interest exists.

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