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Joint impact of early life adversity and COMT Val158Met (rs4680) genotypes on the adult cortisol response to psychological stress

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Abstract

Objective—Exposure to stress during critical periods of development can diminish stress reactivity by the hypothalamic-pituitary-adrenocortical axis. Genetic characteristics may further modify this effect of early adversity, leading to a gene-by-environment ($G \times E$) interaction on stress reactivity in adulthood. Val-allele carriers of a common polymorphism of the *COMT* gene (Val158Met, rs4680) have rapid removal of catecholamines in the prefrontal cortex, limbic system, and reward centers. Carriers of the Val and Met alleles may therefore respond differently to the environment and differ in the long-term impact of exposure to early life adversity (ELA).

Methods—We measured saliva cortisol reactivity to public speaking and mental arithmetic stress in 252 healthy young adults exposed to low, medium, and high levels of ELA and who were genotyped for the Val158Met polymorphism.

Results—Cortisol responses showed a $G \times E$ interaction, $F(4, 243) = 2.78, p = .028$: simple effects tests showed that Met/Met carriers had progressively smaller cortisol responses with

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greater levels of ELA. In comparison, Val/Val homozygotes had blunted responses that did not vary with ELA exposure.

Conclusions—Met/Met homozygotes appear sensitive to stressful events in childhood and adolescence, leading to environmental programming of the stress axis. Glucocorticoid responsivity may represent a common pathway revealing targeted genetic vulnerabilities to the long-term effects of early life stress. The results suggest further $G \times E$ studies of ELA are warranted in relation to health behaviors and health outcomes in adulthood.

Keywords

cortisol; stress; early life adversity; dopamine; catecholamine; genotype; catechol-O-methyltransferase

INTRODUCTION

Exposure to stress during childhood and adolescence may modify the stress reactivity of the hypothalamic-pituitary-adrenocortical axis in adulthood (1), and this sensitivity to early life adversity (ELA) may be regulated in part by the differences in the availability of catecholamines in the central nervous system. The enzyme catechol-o-methyltransferase (COMT) is responsible for breakdown of catecholamines (2, 3) in the brain's prefrontal cortex, limbic system, and reward structures (4–7), and functional variation in COMT may therefore contribute to individual differences in responses to the environment, with implications for cortisol and heart rate responses to emotional stress.

A phylogenetically ancient single nucleotide polymorphism of the *COMT* gene (rs4680), common in human and hominoid ape lineages, results from a functional substitution of the amino acid valine for methionine at codon 158 (Val158Met) (8, 9). The Val158 COMT enzyme is thermally more stable than the Met158 version, and catecholamine breakdown is about 40% more efficient in Val/Val homozygotes (8, 10). Met carriers therefore have greater dopamine availability in the prefrontal cortex and limbic system, brain regions responsible for cognitive function, regulation of affect and direction of motivated behavior (11–14). Met carriers perform better on tests of attention, working memory, and decision-making (15–19), although not all studies are in agreement (20). Despite these cognitive advantages, Met/Met homozygotes are more anxious, sensitive to painful stimuli (21), reactive to emotional faces (22, 23), and they have larger subjective and physiological responses to psychosocial stress (24, 25). The respective cognitive and affective characteristics of Val- and Met-allele carriers suggests potential differences between these groups in the long-term impact of the individual's early environment.

The first human studies to document $G \times E$ interactions found that childhood maltreatment could modify adult behavior and affective disposition in genetically vulnerable persons (26, 27). The striatum and prefrontal cortex are highly sensitive to the environment, and their functional characteristics are modifiable by early experience (1, 7, 28, 29). Given that Met-allele carriers are attentive to environmental inputs and also emotionally reactive (16, 21, 22, 24), we speculated that Val- and Met-allele carriers may be differentially sensitive to the long-term effects of ELA on the HPA and autonomic responses to stress (30). Cortisol stress

reactivity was reportedly diminished in children undergoing current life stress exposure or who were COMT Val/Val carriers (31), although no $G \times E$ interaction was seen. In the Oklahoma Family Health Patterns cohort, exposure to ELA leads to progressively diminished cortisol and heart rate reactivity to psychological stress in adulthood (32, 33). In the present analysis, we examined whether the impact of ELA on cortisol and heart rate reactivity would differ as a function of COMT Val158Met genotypes.

Methods

Participants

Participants were 252 healthy young adults participating in the Oklahoma Family Health Patterns (OFHP) project (32) who had been genotyped for the COMT Val158Met polymorphism along with ancestry informative markers (AIMS) and had sufficient background data to compute ELA scores. Each participant signed an informed consent form approved by the Institutional Review Board of the University of Oklahoma Health Sciences Center and the VA Medical Center, Oklahoma City, Ok, USA, and was given financial compensation.

Inclusion and exclusion criteria—Participants were 18–30 yr-old men and women recruited from the community who were in self-reported good health. Prospective volunteers were excluded if they had: a mental age score < 20 yr on the Shipley Institute of Living Scale (34); a history of alcohol or drug dependence; diagnostic threshold for substance abuse within the past 2 mo; a positive urine screen for drugs of abuse (iCup, Instant Technologies, Norfolk VA) or breath-alcohol test on days of testing; a history of Axis I disorder, other than depression > 60 days prior, using the Diagnostic and Statistical Manual of Mental disorders, 4th ed. (35) based on the CDIS-4 interview (36); had a body mass index > 30 kg/m²; needed prescription medications other than hormonal contraceptives, or had a current medical disorder. Women all had negative urine pregnancy tests at the time of testing. Smoking and smokeless tobacco use were not exclusionary.

ELA assessment—ELA was derived from C-DIS-IV items that are closely similar to the adverse life events assessed retrospectively in studies by Caspi (26, 27) as follows: Physical or Sexual Adversity (“Have you ever been mugged or threatened with a weapon or experienced a break-in or robbery?” “Have you ever been raped or sexually assaulted by a relative?” “Have you ever been raped or sexually assaulted by someone not related to you?”) and Emotional Adversity (“Before you were 15, was there a time when you did not live with your biological mother for at least 6 months?” “Before you were 15, was there a time when you did not live with your biological father for at least 6 months?”). Each person was assigned to an ELA group based on 0, 1, or 2 reported adverse events. Levels of ELA in the present population are considered to be normative, and therefore nontraumatic, because selection criteria excluded persons meeting diagnostic criteria for posttraumatic stress disorder or current major depression. In a separate subset of 334 persons in the OFHP, the number of reported ELA events was significantly correlated with total scores on the Childhood Trauma Questionnaire (Pearson $r = .54$, $p < .0001$) and on each of its 5 subscales (Pearson $r_s = .37$ to $.44$, $p_s < .0001$).

Study Design and Procedure

Participants passing an initial telephone screen underwent detailed assessments at the laboratory and were then tested on a 2-day stress protocol (37). The lab screening was conducted by a trained interviewer supervised by a licensed clinical psychologist and included the C-DIS-IV interview and qualifications for inclusion in the final sample. Participants visited the lab twice more for a stress reactivity protocol including a day of public speaking and mental arithmetic challenges followed by a resting control day, as described elsewhere (32, 37).

Stress procedure—Lab sessions were held at 9:00 am or 1:00 pm, with the time held constant for each subject. Stress testing lasted 105 min, including a resting baseline in a seated position (30 min) followed by simulated public speaking (30 min) and mental arithmetic (15 min) and a 30-min resting recovery period as described elsewhere (37, 38). The resting control day involved sitting for 105 min during the same time of day while reading general interest magazines and watching nature videos. Participants reported their level of perceived activation and distress on a set of 9 point scales at the end of the baseline and stress periods (39).

Saliva samples for cortisol determination were collected using Salivettes at 9 times across each day including: 2 at home (upon awakening and at bedtime) and 7 in the lab (3 prestress, 3 during the stress protocol, and 1 during recovery). Cortisol responses to the stressor were computed as the difference between the mean of the 3 values obtained during the stress protocol and the corresponding values on the resting control day (37). Heart rate was monitored every 2 min along with blood pressure measurements using an automated monitor (Critikon, Dinamap).

Cortisol

After data collection, the Salivettes were centrifuged at 4200 RPM for 20 min. The saliva was transferred to cryogenic storage tubes and placed into a -70°C freezer until shipping. Assays were conducted by Salimetrics (State College, PA, USA) where the saliva free cortisol concentrations were quantified using a competitive enzymatic immunoassay (40). The assay has a sensitivity of $< .083\text{ }\mu\text{g/dL}$ and an interassay coefficient of variation of $< 6.42\%$.

Genotyping

Genomic DNA was prepared from saliva collected by passive drool into an Oragene collection and preservation kit (DNA Genotek, Inc., Kanata, Ontario, Canada). DNA samples were genotyped with the Illumina OmniExpress array using standard protocols. Samples with call rates below 95% were excluded and randomly selected samples showed an average reproducibility of 99.998%. The genotype completion rate was 0.993.

Assessment of population stratification using ancestry informative markers (AIMS)—A panel of 2491 single nucleotide polymorphisms (SNPs) from the Illumina OmniExpress array was selected as an ancestry panel based on the following criteria: (1) large differences in the reference allele frequency of pairwise SNPs from the HapMap

Project between African, Chinese and European populations; (2) mapping on different chromosomes and with no two SNPs within 10 Kb of each other; and (3) shared by both Illumina Human Hap550v3 and HumanOmniExpress-12v1 array. Individual ethnic factor scores corresponding to geographical regions: Africa, Europe, Middle East, Central Asia, Far East Asia, Oceania, and America, were estimated using STRUCTURE v2.3 software using a 6-factor solution and a reference set of 1,051 participants representing 51 populations worldwide (CEPH population) as a reference (<http://www.cephb.fr/HGDP-CEPH-Panel>). Our dataset was predominantly of European origin, with mean (SD) and median European ancestry being 0.89 (0.19) and 0.95 in this sample. Twenty participants had European ancestry scores < 0.50. Of these, 16 were of African ancestry and 4 had Native American ancestry. Genotypes for the COMT Val158Met (rs4680) polymorphism were available on the OmniExpress array and were in Hardy Weinberg Equilibrium in the overall sample ($p = 0.57$). Test-retest accuracy of SNPs on this array was $r > .993$.

Data Analysis

Cortisol responses to stress were then calculated as the average of the three samples taken during the stress period on the stress day (STR1, STR2, STR3) minus the same three samples taken on the rest day. Cortisol data were analyzed by a general linear model including: Genotype (Met/Met, Val/Met, Val/Val), ELA (0, 1, 2), and the $G \times ELA$ interaction term. The significant interaction was deconstructed by simple effects tests to compare subgroups: 1) the three genotypes were compared at each level of ELA, and 2) the three levels of ELA were contrasted within each genotype. We tested potential confounders as covariates in the above analysis, including: sex, age, family history of alcoholism, time of testing, mu-opioid receptor polymorphism *OPRM1* A118G (41), and European and African ethnic factor AIMS scores, by entering each individually into the model. The data set did not permit simultaneous inclusion of these covariates. None of them influenced the results, and accordingly, the unadjusted F ratios are reported here. Type III sums of squares were used to ensure independence of individual F ratios. Tests were considered statistically significant if $p < 0.05$. Analyses were conducted using SAS software 9.2 (Copyright, SAS Institute Inc., Cary, NC, USA).

Results

Demographics for the COMT Val158Met genotype (Met/Met, Val/Met, Val/Val) groups are shown in Table 1. The Val/Val homozygotes had lower European ancestry scores than the other two genotype groups, and reported greater frequencies of ELA 2.

G × ELA Analyses

Subjective states—As a check on the perceived impact of the stressors, we examined participants' reports of Activation and Distress provided at the end of the Baseline and Stress periods in a model including the 3 COMT genotypes $\times$ 3 ELA groups $\times$ 2 Time Periods (Table 2). Significant Periods effects showed increases in feelings of Activation (from 3.49 to 4.96, $F_{2, 243} = 140$, $p < .001$) and Distress (from 2.49 to 3.41, $F_{2, 243} = 92$, $p < .001$), with no ratings differences seen for the ELA or COMT genotype groups or for the interaction.

Cortisol and heart rate responses—Since physiological responses may be influenced by baseline levels, we examined the cortisol diurnal curves for the three genotype groups. As shown in Figure 1, top panel, the three genotype groups had nearly identical patterns of cortisol secretion across the rest day of the study, indicating equivalent levels of HPA axis activity on a normal day. Cortisol responses to stress were then calculated as described, therefore representing difference scores.

The bottom panel of Figure 1 shows the stress day, indicating small cortisol responses in the Val/Val group and larger ones in the Met/Met group, although this group effect was nonsignificant, $F(2, 244) = 0.46, p > .60$, partial $\eta^2 = .004$. In contrast, persons with greater ELA exposure had progressively smaller cortisol responses, $F(df = 2, 244) = 4.56, p = .011$, partial $\eta^2 = .037$, and we observed a significant $G \times ELA$ interaction, $F(df = 4, 244) = 2.78, p = .028$, partial $\eta^2 = .045$, suggesting that effect of ELA on adult cortisol responses depends in part on the person's genotype. We followed with uncorrected post hoc tests to examine the interaction more fully. The effect of 0, 1, and 2 reports of ELA on cortisol stress response was greatest in Met/Met homozygotes, $F(2, 243) = 4.02, p = .023$ (Figure 2, top left panel), less prominent in Val/Met heterozygotes, $F(2, 243) = 2.88, p = .059$, and nonsignificant in Val/Val carriers, $F(2, 243) = 2.40, p = .10$. As shown in the bottom panel of Figure 2, in the absence of ELA exposure ($ELA = 0$) the Val/Val genotype showed the smallest CORT responses and the Met/Met genotype had the largest, $F(2, 243) = 7.80, p < .001$, but this genotype difference dissipated in the face of higher levels of ELA exposure ($p = 0.15$).

HR response to stress was significantly lower in persons with greater levels of ELA exposure, $F(2, 243) = 3.60, p = .029$, consistent with a prior report (1). In contrast to the CORT results, we observed no differences in HR response across genotypes, $F(2, 243) = 1.59, p = .21$, or in the $G \times ELA$ interaction, $F(4, 243) = 1.08, p = .37$.

Discussion

The experience of stress during critical periods of development can adversely affect health behaviors in adulthood (42), and genetic vulnerabilities may enhance these effects (26, 27). Exposure to ELA may lead to diminished stress responses in otherwise healthy young adults (1, 43), although carriers of specific genotypes may respond differently to ELA history (26, 27). We tested the joint impact of ELA and the COMT Val158Met (rs4680) polymorphism on stress cortisol and heart rate reactivity in healthy young adults participating in the OFHP. There were two observations of interest, as shown in Figure 2: First, persons carrying the Met allele appeared to be sensitive to their history of ELA such that Met/Met and Val/Met carriers had diminishing cortisol responses with increasing exposure to ELA, consistent with a gene-dose effect on ELA sensitivity. Second, carriers of the Val allele did not show an effect of prior exposure to ELA on acute responses to stress. These findings complement a study of *COMT* genotype and life stress in children (31) in which cortisol reactivity was lower in children undergoing greater daily stress exposure and also in the Val/Val carriers, although no $G \times E$ interaction was found. The present study extends these findings to a larger sample consisting of adults and shows the potential for a greater impact of ELA in carriers of the *COMT* Met allele relative to their Val counterparts. However, no such effects

were seen in reports of subjective responses to the stressor or in heart rate reactivity, suggesting a specific environmental modification of the glucocorticoid stress response. These findings suggest directions for future work.

The present results and prior work from the OFHP study suggest pleiotropic effects of ELA in adulthood, including diminished cortisol and HR reactivity to stress (44), altered decision-making and cognitive function (32), and unstable regulation of affect (45) irrespective of genotype. ELA also modifies cortisol regulation at the cellular level through differential expression of molecular cochaperones necessary for cortisol actions at the cell nucleus (46–48). The present results indicate that Met-allele carriers may be differentially responsive to the impact of prior ELA while Val-allele carriers may be relatively immune to such early exposure. In both instances, blunted cortisol responses to stress may have significant implications for regulation of glucocorticoid pathways in the central nervous system and their secondary effects on other systems throughout life (49–52) with implications for health.

We also examined the diurnal pattern of cortisol secretion, in the absence of stress, to gain additional insight into the source of the differences stress reactivity in this study. We were able to rule out variations in basal cortisol secretion as responsible for the $G \times E$ interaction since secretion patterns were nearly identical for the Met/Met, Val/Met, and Val/Val genotypes (Figure 1, Top panel) and for the ELA groups (not shown). These equivalent patterns of diurnal secretion suggest comparable levels of intrinsic HPA regulation in the absence of stress. This implies that stress reactivity differences are likely to represent modifications in strength of inputs originating above the HPA during acute stress episodes. In addition, the genotype and ELA groups reported experiencing similar increases in activation and distress during the stress protocol (Table 2), suggesting that cortisol stress reactivity did not vary due to altered interpretation of the stressors. Instead, the $G \times E$ effect may represent intrinsic alterations in neuronal systems regulating the cortisol stress response. In one postmortem study, COMT Val-allele carriers differed from their Met counterparts in *COMT* RNA expression in the prefrontal cortex, limbic system, and striatum (10). Such neuronal differences between the genotypes may potentially modify cortisol stress reactivity as a result of exposure to ELA.

Although our results document $G \times E$ variations in the central feed-forward processes that produce the cortisol stress response, differences in circulating cortisol following a stress episode also affect the adequacy of regulatory feedback to the central nervous system, with implications for long-term regulation of adaptive behavior (53, 54). The prefrontal cortex, limbic system, and striatum are richly supplied by glucocorticoid receptors (53), and these receptors regulate cellular function in response to cortisol feedback following acute stress episodes. Stress levels of cortisol feedback acutely modify activation at the amygdala and hippocampus by way of cell membrane receptors (51, 55, 56), and produce long-term effects, including long term memory (50), through altered gene expression.

ELA and altered cortisol reactivity may have implications for a range of effects in adulthood. Exaggerated and strongly diminished cortisol responses both represent departures from normal homeostatic regulation (37), with possible consequences for long-term health

and behavioral adaptation (57). Miller and Chen comment that early experience leaves a “biological residue” that persists into adulthood and may affect systems relevant for health and disease (58). Emerging work points to ELA and negative effects on adult health behaviors and outcomes, as indicated in the important studies of adverse childhood experiences (42). Given cortisol’s role in regulating activity in the central nervous system, normal cortisol responses to stress are central to healthy behavioral adaptation to demands from the environment (59, 60). Diminished glucocorticoid responses may accompany somatic disorders involving altered regulation of immune system function and enhanced inflammatory processes (58). Several lines of evidence point to ELA and diminished cortisol responses being associated with behavioral disorders including disinhibitory behavioral characteristics and vulnerability to alcohol and other substance use disorders (33, 61–66).

Limitations

Due to the modest sample size, we were unable to pursue promising $G \times G$ interactions that suggest directions for future research on health and behavior. For example, *COMT* genotypes may interact with other genetic polymorphisms affecting glucocorticoid regulation (67) or opioid receptor function (41). For example, persons carrying different *COMT* polymorphisms also differ in occupancy of central mu-opioid receptors during application of painful stimuli (21, 68), and this same mu-opioid receptor polymorphism contributes to sex differences in cortisol response to acute stress and to naltrexone blockade (41) leading to possible sex differences in reward mechanisms associated with dopaminergic function. As already noted, polymorphisms of glucocorticoid co-chaperones affect the glucocorticoid receptor pathway and result in differential sensitivity to ELA, including changes in working memory and cardiac responses to stress (67) and these too may interact with altered central dopamine activity. Serotonin receptor polymorphisms may cause variations in cortisol response to acute stress (69), and a polymorphism in the promoter region of the serotonin transporter gene may modify regulation of affect and overt behavior (70), again having possible interactions with *COMT* Val158Met genotypes.

This study shares limitations with others of its type. The data set is small for a candidate $G \times E$ study and limited statistical power raises the possibility of a Type I error, as has been found in a majority of published $G \times E$ studies (71). This concern is mitigated to a degree by two considerations: (a) Existing evidence suggests a high prior probability that the present $G \times E$ finding may be true. (b) We followed the recommendations by Moffitt, Caspi, and Rutter in the $G \times E$ design and analysis (72). Moreover, the $G \times E$ effect yielded a partial $\eta^2 = .045$, accounting for 4.5% of the variance, suggesting a small-to-medium effect size (73), boosting confidence in this finding. Nevertheless, we emphasize that the present result should be considered provisional prior to replication with independent datasets. Due to the sample size, we were unable to test for the simultaneous effects of multiple confounders or pursue promising ELA effects in relation to $G \times G$ interactions. The sample was selected for an absence of psychiatric disorders, and the results therefore apply only to healthy individuals.

Conclusion

The cortisol response to psychological stress may represent a common pathway for observing genetic vulnerabilities to the long-term effects of early life adversity. The *COMT* Val158Met (rs4680) polymorphism appears to represent one source of genetic vulnerability to childhood adversity. Met/Met carriers had diminished cortisol reactivity if exposed to early adversity, while Val/Val carriers appeared unaffected. The differential impact of ELA on cortisol reactivity in adulthood may affect key glucocorticoid regulatory pathways and therefore bear implications for health and health behaviors throughout life.

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Abbreviations

AIMS	ancestry-informative markers
CDIS-4	computerized diagnostic interview system for Diagnostic and Statistical Manual IV diagnosis of psychiatric disorders
COMT	catechol-O-methyltransferase
E	environment
ELA	early life adversity
G	genotype
HPA	hypothalamic-pituitary-adrenocortical
HR	heart rate
MET	methionine
OFHP	Oklahoma Family Health Patterns project
SD	standard deviation
SEM	standard error of the mean
SES	socioeconomic status
SNP	single nucleotide polymorphism
VA	Veterans Administration
VAL	valine

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Figure 1. Cortisol saliva measurements at home and during visits to the laboratory on a resting control day (top panel) and during exposure to public speaking and mental arithmetic stress (lower panel). Cortisol measurement time points are described in the text.

Figure 2.

Cortisol saliva responses to stress. Bars represent means $\pm$ SEM of difference scores calculated from cortisol values on a rest day subtracted from values taken at the same times during a mental stress protocol on a different day. Top panel shows data arranged by genotypes of the Val158Met, rs4680, polymorphism of the *COMT* gene. The bottom panel shows the same data arranged by early life adversity exposure group (0, 1, and ≥ 2 stressful life events during childhood and adolescence). Cortisol measurement time points are described in the text.

Table 1

Demographics for COMT genotypes

Genotype	MET/MET	VAL/MET	VAL/VAL	<i>p</i> -value
N = 252	75	129	48	
Sex (% F)	55	62	55	0.56
Age	24.2 [0.33]	23.4 [0.24]	23.3 [0.43]	0.12
SES	48.8 [1.58]	46.9 [1.11]	46.2 [1.80]	0.49
Education (yr)	16.0 [0.19]	15.6 [0.16]	15.3 [0.27]	0.07
AIMS (% Eur)	93 [2]	92 [1]	83 [4]	0.004
ELA (% 2)	11	17	27	0.03

Note: Entries show Mean ($\pm$ SEM) unless otherwise noted. No significant ELA $\times$ Genotype interactions were found, and the *p*-values refer to genotype comparisons only.

p-values refer to *F*-ratio or Chi-squared comparison across genotype groups.

SES = Socioeconomic Status. AIMS = Ancestry Informative Markers (% with European ancestry markers). ELA = Early Life Adversity.

Table 2

Self-reports of activation and distress for adversity and genotype groupings

	Early Life Adversity			F-ratio	p-value
	0	1	2		
Distress					
Baseline	2.54 [0.1]	2.37 [0.1]	2.58 [0.2]	0.05	0.82
Stress	3.39 [0.1]	3.27 [0.2]	3.78 [0.3]	1.05	0.31
Activation					
Baseline	3.38 [0.2]	3.56 [0.2]	3.54 [0.2]	0.57	0.45
Stress	5.06 [0.1]	4.81 [0.2]	4.89 [0.2]	0.84	0.36
COMT Val158Met Genotype					
	MET/MET	VAL/MET	VAL/VAL		
Distress					
Baseline	2.44 [0.1]	2.54 [0.1]	2.47 [0.2]	0.07	0.79
Stress	3.43 [0.2]	3.44 [0.1]	3.31 [0.2]	0.78	0.38
Activation					
Baseline	3.66 [0.2]	3.41 [0.1]	3.43 [0.3]	0.14	0.71
Stress	5.00 [0.2]	4.90 [0.1]	5.07 [0.2]	0.02	0.89