発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
野田隆政.	光トポグラフィによるうつ病診断.	医学のあゆみ	244	425-431	2013
野田隆政	Bipolar Depressionの診断と治療～最近の話題～ NIRSの有用性	Depression Frontier	11	15-22	2013
福田正人，吉田寿美子，杉村有司，小川勝，大渓俊幸，樋口智江，内山智恵，安井臣子	光トポグラフィー検査（NIRS）による脳機能測定.	. 検査と技術	40	182-188	2012
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Ⅳ.　研究成果の刊行物・別刷

Psychiatry and Clinical Neurosciences 2012; **66**: 276–284 doi:10.1111/j.1440-1819.2012.02349.x

Regular Article

Differential relationships between personality and brain function in monetary and goal-oriented subjective motivation: Multichannel near-infrared spectroscopy of healthy subjects

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Aim: To examine relationships between personality traits and cerebral cortex reactivity under different motivating conditions.

Methods: Relationships between personality traits assessed using the NEO Personality Inventory–Revised (NEO-PI-R) and cerebral cortex reactivity during a verbal fluency task monitored using multichannel near-infrared spectroscopy (NIRS) were examined under three different motivational conditions: control, monetary reward, and goal-oriented, in healthy young male volunteers.

Results: Significant correlations between cerebral cortex reactivity and personality traits were found in the frontopolar region: a positive correlation with agreeableness and a negative correlation with the neuroticism and conscientiousness scores of the NEO-PI-R under the three motivational conditions. Higher scores for agreeableness were more strongly associated with a greater increase in total hemoglobin concentration ([total-Hb]) under the goal-oriented and control conditions than under the monetary reward condition. In addition, higher scores for neuroticism were more strongly associated with a greater increase in deoxygenated hemoglobin concentration ([deoxy-Hb]) under the monetary reward condition than the goal-oriented condition, and higher scores for conscientiousness were more strongly associated with a greater increase in [deoxy-Hb] under control conditions than under the goal-oriented condition.

Conclusion: Using multichannel NIRS, certain personality traits of the big-five model are related to frontopolar reactivity. These relationships vary depending on the motivational condition when brain functions are monitored: agreeableness, neuroticism, and conscientiousness are all related to frontopolar reactivity depending on the motivational condition.

Key words: brain activation, near-infrared spectroscopy, personality characteristic, subjective motivation.

PERSONALITY IS DEFINED as ingrained patterns of thought, feeling, and behavior characterizing an individual's unique lifestyle and model of adaptation resulting from constitutional factors, development, and social experience. It has conventionally been conceptualized as consisting of several factors or dimensions. Representative examples of hypothesis-driven and empirically based major personality models are the Temperament and Character Inventory and the NEO Personality Inventory–Revised (NEO-PI-R), respectively.[1,2]

The brain substrates associated with the five dimensions of the NEO-PI-R have been studied in

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Received 28 September 2010; revised 7 October 2011; accepted 12 October 2011.

healthy subjects. The neuroticism score of the NEO-PI-R was negatively correlated with the ratio of the brain volume to the remainder of the intracranial volume on magnetic resonance imaging (MRI) and with insula metabolism on positron emission tomography (PET).[3,4] The extraversion score was positively correlated with orbitofrontal cortex metabolism on PET and with increased cerebral blood flow in the anterior cingulate gyrus, temporal lobes, and posterior thalamus on single-photon emission computed tomography (SPECT).[4,5] Significant correlations have also been observed in patients with psychiatric disorders: the depression score (one of the subscales of neuroticism) was correlated with MRI abnormalities in early-onset Alzheimer's disease,[6] the extraversion score was correlated with gray matter volume loss in the right posterior fusiform gyrus in patients with chronic schizophrenia,[7] and the agreeableness score was positively correlated with right orbitofrontal lobe volume and negatively correlated with left orbitofrontal lobe volume in frontotemporal dementia patients.[8]

Near-infrared spectroscopy (NIRS) is a recently available functional brain imaging technique in which cerebral blood volume (CBV) changes are monitored by measuring increases in oxygenated hemoglobin concentration ([oxy-Hb]) and decreases in deoxygenated hemoglobin concentration ([deoxy-Hb]). NIRS is particularly suitable for personality studies because it enables measurement in a natural setting, compared with other functional brain imaging techniques such as PET and functional MRI.[9–11] For example, NIRS enables examination of subjects in a sitting position, with their eyes open, and while speaking using a small apparatus by their bedside, with a fine time resolution.[12] Due to its technical advantages, NIRS addresses one of the main problems of functional neuroimaging personality studies: lack of a natural setting during neuroimaging.

Here, we examined differential relationships between personality traits assessed using the NEO-PI-R and frontal and temporal lobe activation during a verbal fluency task (VFT) using multichannel NIRS in healthy male subjects. Activation changes in brain functions were able to be monitored in a natural setting. In addition to the usual task-activated condition, frontal lobe and temporal lobe activation was also examined under two motivationally modified versions of the task-activated condition: a monetary reward condition and a goal-oriented condition. These conditions were used because human behaviors are, in general, motivated by reward and social interaction, and because task-induced brain activation is considered to be modified by the motivational state of the subject at the time of examination and hence to be differentially related to personality depending on the type of motivation.[13]

We hypothesized that the personality dimensions of the NEO-PI-R would be correlated with brain activation, and that these relationships would vary between the monetary reward, goal-oriented, and control conditions.[14,15] All of the dimensions of the NEO-PI-R could be correlated with brain activation, because motivation is assumed to consist of various aspects of brain function. For example, personality dimensions reflecting interpersonal relationships such as extraversion and agreeableness could be positively correlated with brain function, especially under the goal-oriented condition, because subjects with high extraversion or agreeableness are assumed to be more motivated in a natural setting with an examiner. Personality dimensions reflecting interpersonal relationships and emotional features such as openness and neuroticism could be positively and negatively correlated with brain function, respectively, particularly under the monetary reward and the goal-oriented conditions, because motivation is considered to be related to openness and to be decreased during high-tension situations such as an examination. In addition, personality dimensions reflecting an effort-related nature such as conscientiousness could be positively correlated with brain function, because motivation is closely correlated with effort.

METHODS

Subjects

Thirty-six healthy volunteers participated in this study. All of the subjects were male (mean age, 23.6 ± 2.75 years; range, 19–29 years) and were scored as right-handed using the Edinburgh Handedness Inventory scale.[16] They were medics or medical department students with no history of any major psychiatric disorder, neurological disorder, substance abuse, head injury, or major physical illness, and they were not on any psychotropic medications at the time of the study. The subjects abstained from alcohol for at least 12 h prior to the NIRS measurements. This study was approved by the Institutional Review

Board of Gunma University Graduate School of Medicine. Written informed consent was obtained from all of the subjects prior to the study.

Assessment of personality characteristics

The personality characteristics of the subjects were assessed using the Japanese version of the NEO-PI-R (Tokyo Shinri, Tokyo, Japan).[2] The NEO-PI-R was undertaken by all subjects after the NIRS measurements using a standardized assessment protocol in which subjects completed a personality characteristics questionnaire.

Verbal fluency task and motivational conditions

A modified letter version of a verbal fluency task was used as the activation task for measurement of CBV changes. Subjects sat in a comfortable chair in a bright room with their eyes open throughout the measurements. The verbal fluency task consisted of a 30-s pre-task baseline, a 60-s verbal fluency period, a 70-s post-task baseline, and 60-s relaxation period.

Each subject underwent three consecutive sessions of the verbal fluency task with different motivational conditions, with a rest of >5 min between sessions: control, monetary reward, and goal-oriented conditions. We measured only one activation period per motivational condition, because repeating the measurement dampens the effect of personality and reward on brain activation. Under the control condition, the subjects were instructed to perform the verbal fluency task without any motivational condition, looking at a plus symbol on the CRT monitor in front of the subject. Under the monetary reward condition, the subjects were instructed before the session that they would be paid 100 yen for each correct word generated. The subjects looked at a plus symbol on the CRT monitor during the session as under the control condition. Under the goal-oriented condition, the subjects were motivated to generate the expected number of words by looking at the CRT monitor: on the CRT monitor, the number of words generated was overtly displayed as the number of accumulated green rectangles, and the expected number of words was shown as a pink line above the accumulated rectangles. The subjects were instructed to continue the task even when they reached the goal line. The order of the three syllable sets (six combinations) and the order of the three motivational conditions (six combinations) were completely counterbalanced among the 36 (6×6) subjects.

Assessment of subjective changes induced by motivational condition

Subjective changes induced by the motivational conditions were assessed immediately after each NIRS measurement condition using a questionnaire that the authors developed for this study. The questionnaire consisted of six items: motivation, effort, concentration, tiredness, difficulty, and fatigue, and the subjects were required to score each item from 5 (strongly agree) to 1 (strongly disagree).

NIRS measurements

Changes in [oxy-Hb], [deoxy-Hb], and total hemoglobin ([total-Hb]; the sum of [oxy-Hb] and [deoxy-Hb]) were monitored using a 52-channel NIRS machine based on the continuous wave method of measurement (ETG-4000; Hitachi Medical, Tokyo, Japan). The NIRS probe holders were placed on the subject's frontal and temporal regions. Hemoglobin concentration changes were measured at 52 measurement points, with the lowest probe line positioned along the T3, F7, Fp1, Fp2, F8, and T4 lines in accordance with the international 10/20 system used in electroencephalography. [Oxy-Hb] and [deoxy-Hb] were calculated based on absorption of near-infrared light of two wavelengths (780 and 830 nm) emitted from the emission probe and detected by the detection probe 3 cm away.

We chose the prefrontal cortex as the measured region because previous studies have reported that the prefrontal cortex was related to personality and motivational conditions.[4,17–19]

Statistical analysis

Task performance and subjective changes induced by the motivational conditions

Task performance and subjective changes induced by the motivational conditions were analyzed using one-way repeated-measures analysis of variance (ANOVA) and the Friedman test, respectively, with 'condition' (the control, monetary reward, and goal-directed conditions) as an independent factor, followed by the post-hoc Wilcoxon test. Pearson's correlations of the NEO-PI-R scores with task performance were also examined.

NIRS data

The channels for which the mean [total-Hb] during the task segment divided by the standard deviation of [total-Hb] during the pre-task segment was <5.0 were excluded from further analysis, because such channels tend to have low signal-to-noise ratios due to the limited near-infrared light detected. Based on this criterion, 29 channels (11, 14, 15, 18, 19, 24–29, 32, 34–40, 42, and 44–52) were retained for further analysis. Channels were generally excluded if the signal was low under at least one reinforcement condition.

[Oxy-Hb] and [deoxy-Hb] measured during the task period were analyzed in three steps. First, channels with significant [oxy-Hb] and/or [deoxy-Hb] changes were identified. The individually averaged [oxy-Hb] and [deoxy-Hb] waveforms were divided into the following three time segments: a pre-task segment for 10 s before the verbal fluency period; a task segment for 60 s during the task period; and a post-task segment for 60 s after the task period. The averages of [oxy-Hb], [deoxy-Hb], and [total-Hb] within these three time segments were calculated and analyzed using one-way repeated measures of ANOVA. The channels were considered to be activated by the verbal fluency task when the segment factor showed a significant effect ($P < 0.05$, ANOVA) and [Hb] during the pre-task and task segments was significantly different, as determined on a post-hoc *t*-test with Bonferroni correction, because these effects were considered to be independent at each channel.

Next, Pearson's correlations for [oxy-Hb], [deoxy-Hb], and [total-Hb] with task performance were conducted. Finally, the mean [oxy-Hb], [deoxy-Hb], and [total-Hb] during the task segments were analyzed using one-way repeated-measures analysis of covariance (ANCOVA) with 'condition' (control, monetary reward, and goal-directed conditions) as an independent factor and the five scores of the NEO-PI-R for 'personality characteristics' (neuroticism, extraversion, openness, agreeableness, and conscientiousness) as covariates, followed by a post-hoc *t*-test. For channels showing statistically significant covariate effects of personality characteristics, the mean [oxy-Hb], [deoxy-Hb], and [total-Hb] during the task segments were analyzed using correlation analysis with the five personality characteristics scores of the NEO-PI-R under each condition. In addition, as a post-hoc test for interaction, for channels showing statistically significant interaction effects for the NEO-PI-R scores with 'condition' (the three conditions), the mean [oxy-Hb], [deoxy-Hb], and [total-Hb] during the task segments were analyzed using one-way repeated-measures ANCOVA with 'condition' (all pairs of conditions: control–monetary reward, control–goal oriented, and monetary reward–goal oriented) as an independent factor and the five scores of the NEO-PI-R for 'personality characteristics' as covariates.

In the second and third steps, channels with significant activation under all three conditions were used for analysis. Correlations and interactions were interpreted as statistically significant only if more than two neighboring channels had significance levels of $P < 0.05$ to exclude the effects of multiple correlations; the probability that three spatially neighboring channels had a significance level of $P < 0.05$ was less than 5% of all possible combinations of three channels among all of the channels with significant activation (maximum for [total-Hb]: $n = 27$).

RESULTS

Comparison of the three conditions

NEO-PI-R scores and subjective changes induced by motivational condition and task performance

The means and SDs for the NEO-PI-R scores were 97.2 ± 19.1 (neuroticism), 103.8 ± 21.1 (extraversion), 116.9 ± 15.0 (openness), 107.8 ± 13.7 (agreeableness), and 102.1 ± 18.5 (consciousness). The means and SDs for task performance and the scores for the subjective changes induced by the motivational conditions were 19.9 ± 5.9 (task performance), 3.6 ± 0.8 (motivation), 3.2 ± 0.9 (effort), 3.5 ± 0.9 (concentration), 2.5 ± 1.1 (tiredness), 3.3 ± 0.6 (difficulty), and 2.2 ± 1.0 (fatigue). Motivation was scored significantly higher under the monetary reward than under the control condition ($Z = -2.48$, $P = 0.013$), and was not significantly different between the goal-oriented condition and the control ($Z = -1.63$, $P = 0.103$) or monetary reward ($Z = -1.03$, $P = 0.302$) conditions. Task performance, however, was not significantly different among the three conditions. The other scores were also not significantly different among the three conditions ($F = 0.093$, $P = 0.911$).

NIRS data

The grand averaged waveforms for [oxy-Hb], [deoxy-Hb], and [total-Hb] during the verbal fluency task under the control, monetary reward, and goal-oriented conditions are shown in Figure 1. During the task period, [oxy-Hb] significantly increased in 27 channels (11, 14, 15, 18, 19, 24–29, 32, 34–40, and 44–51; $F = 9.0–30.2$, $P < 0.001$) under the control condition; in the same 27 channels (11, 14–15, 18, 19, 24–29, 32, 34–40, 44–51; $F = 13.6–49.6$, $P < 0.001$) under the monetary reward condition; and in these 27 channels (11, 14–15, 18, 19, 24–29, 32, 34–40, 44–52; $F = 10.4–35.4$, $P < 0.001$) under the goal-oriented condition. During the task period, [deoxy-Hb] significantly decreased in 22 channels (24–29, 32, 34–40, 44–51; $F = 5.1–33.1$, $P < 0.039$) under the control condition; in 26 channels (14, 18, 24–29, 32, 34–40, 42, 44–51; $F = 4.0–58.9$, $P < 0.031$) under the monetary reward condition; and in 22 channels (24–29, 32, 34–40, 44–46, 48–52; $F = 5.3–42.5$, $P < 0.014$) under the goal-oriented condition. During the task period, [total-Hb] significantly increased in 27 channels (11, 14, 15, 18, 19, 24–29, 32, 34–40, 44–51; $F = 9.6–30.8$, $P < 0.001$) under the control condition; in 27 channels (11, 14, 15, 18, 19, 24–29, 32, 34–40, 44–52; $F = 8.6–33.7$, $P < 0.003$) under the monetary

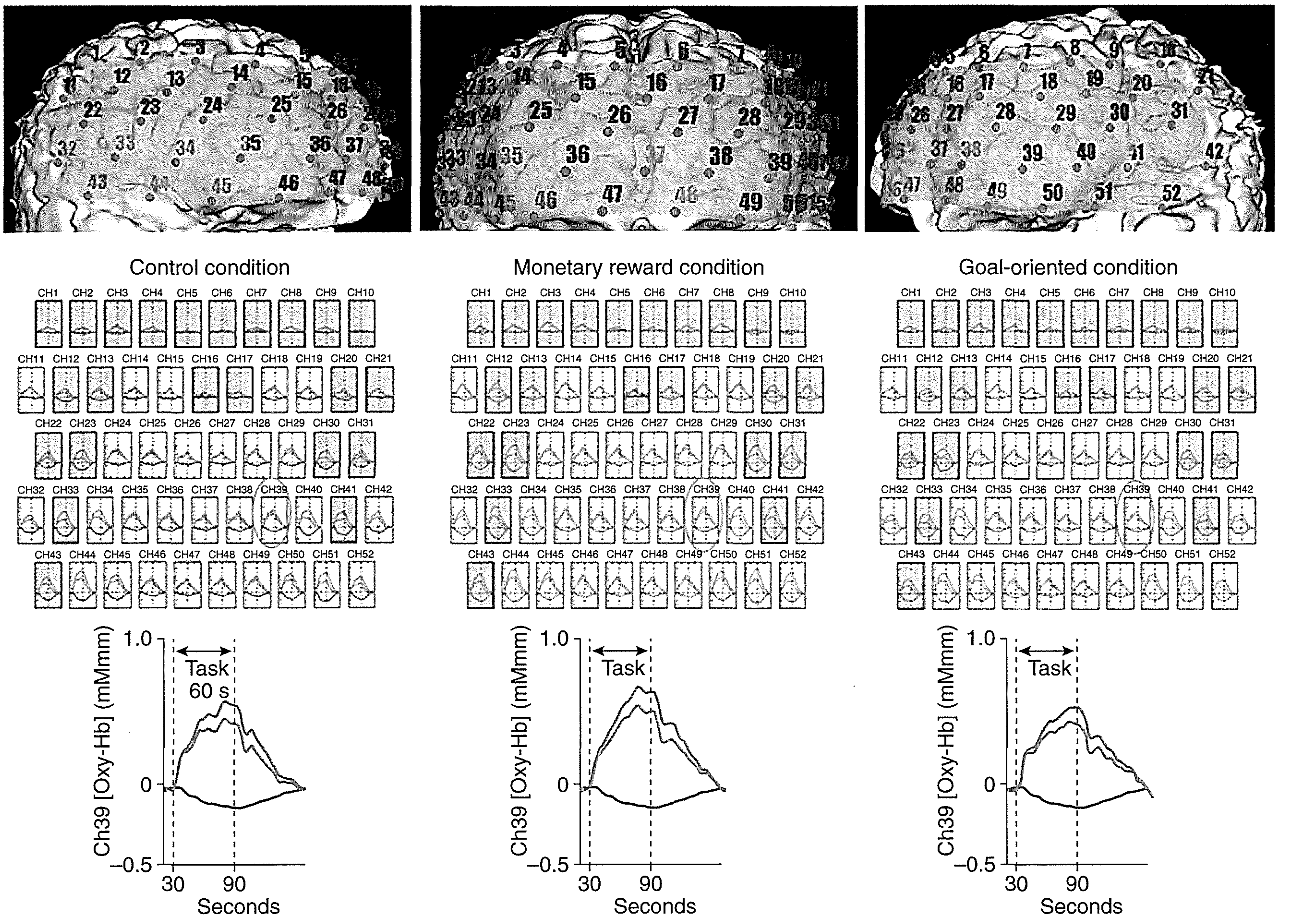

Figure 1. Grand averaged waveforms of hemoglobin concentration changes during the verbal fluency task under the control, monetary reward, and goal-oriented conditions. Grand averaged waveforms of (red) [oxy-Hb], (blue) [deoxy-Hb], and (green) [total-Hb] changes during the verbal fluency task (between the two vertical dotted lines) measured using frontal and temporal probes. (grey fill) Channels with low signal-to-noise ratios. An example of a grand averaged waveform is enlarged below. The upper figures show the measurement positions of the near-infrared spectroscopy machines, superimposed on a magnetic resonance image of a reconstructed cerebral cortex. Ch, channel number.

Table 1. Channels with significant correlations of [oxy-Hb], [deoxy-Hb], and [total-Hb] with task performance

Condition	[Oxy-Hb]	[Deoxy-Hb]	[Total Hb]
Control	**N (ch. 11, 24, 29, 34, 37, 39, 50: $R < 0.332$, $P < 0.048$)**	$R > -0.237$, $P > 0.164$	**N (ch. 24, 29, 32, 34, 37, 39 40, 50: $R < -0.337$, $P < 0.045$)**
Monetary reward	$R < 0.274$, $P > 0.107$	**N (ch. 37: $R = -379$, $P = 0.022$)**	**P (ch. 15: $R = 0.365$, $P = 0.029$)**
Goal-oriented	$R > -0.314$, $P > 0.062$	**N (ch. 26, 27, 36, 37, 38, 48, 49: $R < -0.359$, $P < 0.032$)**	$R > -0.317$, $P > 0.060$

Ch., channel no.; N, negative correlations; P, positive correlations. **Bold**, significant correlation ($P < 0.05$).

reward condition; and in 28 channels (11, 14, 15, 18, 19, 24–29, 32, 34–40, 44–52; $F = 9.9–26.1$, $P < 0.001$) under the goal-oriented condition. One-way ANCOVA demonstrated no significant main effect of the independent variable 'condition': [oxy-Hb], [deoxy-Hb], and [total-Hb] changes during the task period were not significantly different among the three conditions ($F < 3.86$, $P > 0.033$; $F < 4.22$, $P > 0.025$; and $F < 5.37$, $P > 0.010$, respectively) in any channel.

Correlation analysis

Assessment of personality characteristics

None of the NEO-PI-R scores was significantly correlated with task performance under the control, monetary reward, or goal-oriented conditions ($P > 0.073$, $P > 0.095$, and $P > 0.081$, respectively).

NIRS data

[Oxy-Hb] changes were negatively correlated in more than two neighboring channels with task performance under the control condition (ch. 29: $r = -0.346$, $P = 0.039$; ch. 39: $r = -0.338$, $P = 0.044$; ch. 50: $r = -0.346$, $P = 0.039$), but not under the monetary reward condition ($r < 0.274$, $P > 0.107$) or the goal-oriented condition ($r > -0.314$, $P > 0.062$). [Deoxy-Hb] changes were significantly correlated in more than two neighboring channels with task performance under the goal-oriented condition (ch. 26: $r = -0.359$, $P = 0.032$; ch. 27: $r = -0.449$, $P = 0.006$; ch. 36: $r = -0.426$, $P = 0.010$; ch. 37: $r = -0.386$, $P = 0.020$; ch. 38: $r = -0.456$, $P = 0.005$; ch. 48: $r = -0.363$, $P = 0.029$; ch. 49: $r = -0.367$, $P = 0.028$), but not under the control condition ($r > -0.237$, $P > 0.164$) or the monetary reward condition ($r > -0.379$, $P > 0.022$). [Total-Hb] changes were significantly correlated in more than two neighboring channels with task performance under the control condition (ch. 29: $r = -0.356$, $P = 0.033$; ch. 39: $r = -0.350$, $P = 0.036$; ch. 40: $r = -0.337$, $P = 0.045$; ch. 50: $r = -0.371$, $P = 0.026$), but not under the monetary reward condition ($r < 0.365$, $P > 0.029$) or the goal-oriented condition ($r > -0.317$, $P > 0.060$). Table 1 lists channels showing significant correlations of [oxy-Hb], [deoxy-Hb], and [total-Hb] with task performance under three motivational conditions.

Covariate effects of personality characteristics in the ANCOVA were significant for [oxy-Hb] for neuroticism (ch. 18, 28, 29, 39; $F > 4.39$, $P < 0.045$) and agreeableness (ch. 14, 15, 24–26, 35, 39, 40, 50, 51; $F > 4.18$, $P < 0.050$), but were not significant for [deoxy-Hb] for any of the five dimensions. Covariate effects were significant for [total-Hb] for neuroticism (ch. 18, 28, 39; $F > 4.50$, $P < 0.042$), agreeableness (ch. 14, 24–27, 29, 35, 37–40; $F > 4.18$, $P < 0.050$), and conscientiousness (ch. 29, 40, 50; $F > 4.28$, $P < 0.047$) in more than two neighboring channels. Table 2 lists channels having significant correlations of [oxy-Hb], [deoxy-Hb], and [total-Hb] with scores in NEO-PI-R, obtained as significant effects of 'personality' covariates in ANCOVA.

[Oxy-Hb] was positively correlated with agreeableness under the control condition ($r > 0.353$, $P < 0.035$) and the goal-oriented condition ($r > 0.344$, $P < 0.040$), and was negatively correlated with neuroticism under the monetary reward condition (ch. 28: $r = -0.333$, $P = 0.047$) and the goal-oriented condition (ch. 28: $r = -0.388$, $P = 0.019$; ch. 39: $r = -0.329$, $P = 0.050$). [Total-Hb] was positively correlated with agreeableness scores under the control condition ($r > 0.339$, $P < 0.043$) and the goal-oriented condition ($r > 0.399$, $P < 0.016$), and was negatively correlated with neuroticism (ch. 18: $r = -0.343$, $P = 0.041$; ch. 28: $r = -0.343$, $P = 0.041$) and conscientiousness (ch. 40: $r = -0.377$, $P = 0.023$) under the monetary reward condition. Figure 2 shows NIRS channels with significant correlations for

Table 2. Channels with significant correlations of [oxy-Hb], [deoxy-Hb], and [total-Hb] vs. NEO-PI-R score†

	[Oxy-Hb]	[Deoxy-Hb]	[Total Hb]
Neuroticism	**Ch. 18, 28, 29, 39, $F > 4.39$, $P < 0.045$**	$F < 3.46$, $P > 0.073$	**Ch. 18, 28, 39, $F > 4.50$, $P < 0.042$**
Extraversion	**Ch. 24, F = 4.60, $P = 0.40$**	$F < 3.76$, $P > 0.062$	$F < 3.64$, $P > 0.066$
Openness	**Ch. 25, 35, 39, $F > 4.59$, $P < 0.040$**	**Ch. 25, 45 51, $F > 6.43$ $P < 0.017$**	**Ch. 35, 36, 39, $F > 4.45$, $P < 0.043$**
Agreeableness	**Ch. 11, 14, 15, 24, 25, 26, 35, 37, 39, 40, 45, 50, 51, $F > 4.27$, $P < 0.048$**	**Ch. 34, $F = 4.29$, $P = 0.048$**	**Ch. 11, 14, 24, 25, 26, 27, 29, 35, 37, 38, 39, 40, $F > 4.18$,** $P < 0.050$
Conscientiousness	**Ch. 40, 44, 50, $F > 4.18$, $P < 0.050$**	**Ch. 40, $F = 4.33$, $P = 0.046$**	**Ch. 29, 40. 44, 50, $F > 4.28$, $P < 0.047$**

†Obtained as significant effects of 'personality' covariates in ANCOVA. **Bold**, significant correlation ($P < 0.05$). F and P-values are for the significant but the most weak correlation. P and F-values are the largest and smallest, respectively. Ch, channel number; NEO-PI-R, NEO Personality Inventory–Revised.

[Hb] with NEO-PI-R and significant interactions between NEO-PI-R and 'condition'.

Interaction effects between 'condition' and 'personality characteristic' were significant in more than two neighboring channels for [deoxy-Hb] for neuroticism (ch. 25, 26, 36; $F > 3.45$, $P < 0.038$) and conscientiousness (ch. 28, 38, 39; $F > 3.35$, $P < 0.042$), and for [total-Hb] for agreeableness (ch. 19, 27–29, 38–40, 49, 50; $F > 3.43$, $P < 0.039$). Post-hoc ANCOVA showed that higher scores for neuroticism were more strongly associated with a greater increase in [deoxy-Hb] under the monetary reward condition than under the goal-oriented condition ($F > 6.367$, $P < 0.017$), that higher scores for conscientiousness were more strongly associated with a greater increase in [deoxy-Hb] under the control condition than under the goal-oriented condition ($F > 30.0$, $P < 0.033$), and that higher scores for agreeableness were more strongly associated with a greater increase in [total-Hb] under the goal-oriented condition ($F > 5.05$, $P < 0.032$) and control condition ($F > 4.31$, $P < 0.047$) than under the monetary reward condition. Figure 3 shows relationship between agreeableness score and [total-Hb] under control, monetary reward, and goal-oriented conditions in ch. 39.

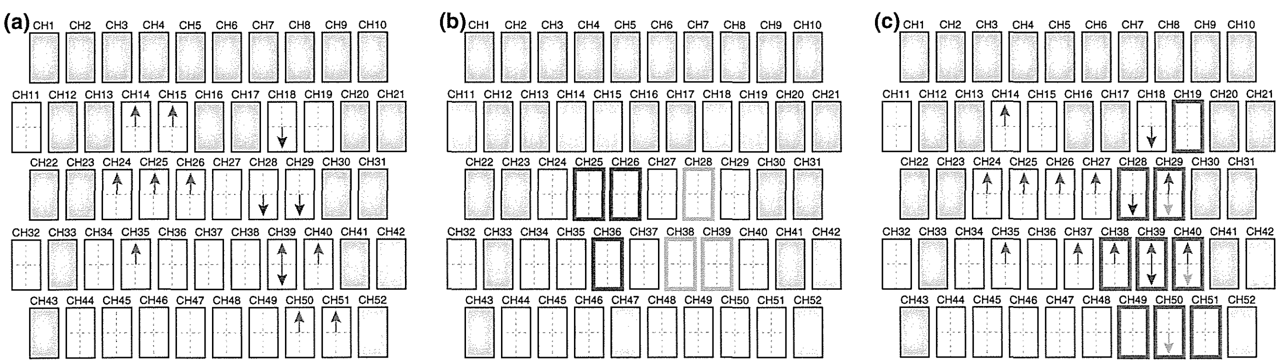

Figure 2. Near-infrared spectroscopy channels with significant correlations for (a) [oxy-Hb] (b) [deoxy-Hb], and (c) [total-Hb] with agreeableness (red arrows), neuroticism scores (blue arrows), and consciousness scores (yellow arrows) on the NEO Personality Inventory–Revised (upward for positive and downward for negative correlations), and those with significant (red outline) interactions between agreeableness and 'condition', (blue outline) interactions between neuroticism and 'condition', and (yellow outline) interactions between consciousness and 'condition' as determined on ANCOVA. (Light blue fill) Channels in which activations of [Hb] were not significant under any of the conditions. Ch., channel number.

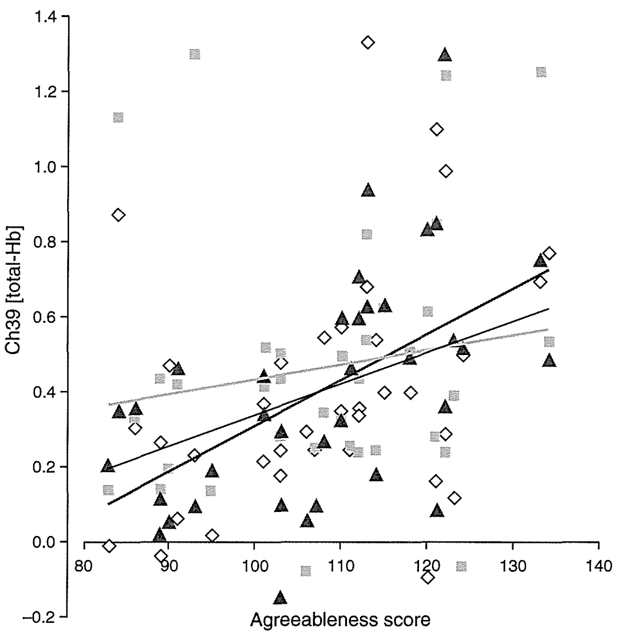

Figure 3. Relationship between agreeableness score and [total-Hb] under (◇) control, (▒) monetary reward, and (▲) goal-oriented conditions in ch. 39, in which their interactions were significant. Ch, channel number.

DISCUSSION

In the present study we examined relationships between personality traits assessed using the NEO-PI-R and cerebral cortex reactivity during a verbal fluency task monitored using multichannel NIRS under three different motivational conditions: control, monetary reward, and goal-oriented, in healthy young male volunteers. The results indicate that (i) subjective motivation for the task was enhanced under the monetary reward condition, but without any improvement in task performance or cerebral cortex reactivity, that is, [oxy-Hb], [deoxy-Hb], and [total-Hb] changes during the task were not significantly different among the three conditions; (ii) cerebral cortex reactivity correlated negatively with task performance under the control condition for [oxy-Hb] and [total-Hb] and under the goal-oriented condition for [deoxy-Hb]; (iii) agreeableness was positively correlated with [oxy-Hb] and [total-Hb], neuroticism was negatively correlated with [oxy-Hb] and [total-Hb], and conscientiousness was negatively correlated with [total-Hb]; and (iv) agreeableness was more strongly associated with a greater increase in [total-Hb] under the goal-oriented and control conditions than under the monetary reward condition, neuroticism was more strongly associated with a greater increase in [deoxy-Hb] under the monetary reward condition than under the goal-oriented condition, and conscientiousness was more strongly associated with a greater increase in [deoxy-Hb] under the control condition than under the goal-oriented condition.

These results suggest that (i) several of the personality traits in the big-five model are related to frontopolar reactivity; (ii) such relationships vary depending on the motivational condition when brain functions are monitored; and (iii) agreeableness, neuroticism, and conscientiousness are related to frontopolar reactivity depending on the motivational condition. The present subjects were psychologically motivated under the motivational condition, but not sufficiently to improve task performance. The advantage of the NIRS technique is that it can monitor brain functions as activation changes in a more natural setting than other neuroimaging methods. We hypothesized that personality dimensions reflecting interpersonal relationships such as extraversion and agreeableness might be positively correlated with brain functions, particularly under the goal-oriented condition, because subjects with high extraversion or agreeableness are assumed to be more motivated in a natural setting with an examiner. Agreeableness was found to be positively correlated with brain functions, particularly under the goal-oriented condition. We also hypothesized that personality dimensions reflecting interpersonal relationships and emotional features such as openness and neuroticism might be positively and negatively correlated with brain functions, respectively, particularly under the monetary reward and goal-oriented conditions, because motivation is considered to be related to openness and to be decreased in high-tension situations such as an examination. Neuroticism was found to be negatively correlated with brain functions, particularly under the monetary reward condition. Last, we hypothesized that personality dimensions reflecting an effort-related nature such as conscientiousness might be positively correlated with brain functions, because motivation is closely correlated with effort. Conscientiousness was found to be negatively correlated with brain functions, particularly under the control condition, contrary to our hypothesis.

These findings suggest that subjective motivation may differentially affect brain functions depending on the motivation of the subjects. Such differential brain activation is, in addition, dependent on personality traits, based on the significant interactions between personality characteristics and motivational conditions for [total-Hb] and [deoxy-Hb]. Thus, subjective motivation was observed to be influenced by various factors such as brain function, motivational condition, and personality traits. These findings can be applied to motivational procedures in education and rehabilitation in medicine.

Conclusions

Using multichannel NIRS, several of the personality traits in the big-five model were found to be related to frontopolar reactivity. These relationships vary depending on the motivational condition when brain functions are monitored; agreeableness, neuroticism, and conscientiousness are related to frontopolar reactivity depending on the motivational condition.

ACKNOWLEDGMENTS

This work was supported in part by grants from Japan Society for the Promotion of Science (Grants-in-Aid for Scientific Research (B) (No. 23390286) and for challenging Exploratory Research (No. 22659209) to MF), from the Ministry of Health, Labour and Welfare (Health and Labour Sciences Research Grants, Comprehensive Research on Disability, Health and Welfare, No. H23-Seishin-Ippan-002 to MF), and from the National Center for Neurology and Psychiatry (Intramural Research Grant for Neurological and Psychiatric Disorders, no. 21-1 and 23-10 to MF).

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Associations Among Parenting Experiences During Childhood and Adolescence, Hypothalamus-Pituitary-Adrenal Axis Hypoactivity, and Hippocampal Gray Matter Volume Reduction in Young Adults

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Abstract: Recent human studies have indicated that adverse parenting experiences during childhood and adolescence are associated with adulthood hypothalamus-pituitary-adrenal (HPA) axis hypoactivity. Chronic HPA axis hypoactivity inhibits hippocampal gray matter (GM) development, as shown by animal studies. However, associations among adverse parenting experiences during childhood and adolescence, HPA axis activity, and brain development, particularly hippocampal development, are insufficiently investigated in humans. In this voxel-based structural magnetic resonance imaging study, using a cross-sectional design, we examined the associations among the scores of parental bonding instrument (PBI; a self-report scale to rate the attitudes of parents during the first 16 years), cortisol response determined by the dexamethasone/corticotropin-releasing hormone test, and regional or total hippocampal GM volume in forty healthy young adults with the following features: aged between 18 and 35 years, no cortisol hypersecretion in response to the dexamethasone test, no history of traumatic events, or no past or current conditions of significant medical illness or neuropsychiatric disorders. As a result, parental overprotection scores significantly negatively correlated with cortisol response. Additionally, a significant positive association was found between cortisol response and total or regional hippocampal GM volume. No significant association was observed between PBI scores and total or regional hippocampal GM volume. In conclusion, statistical associations were found between parental

Additional Supporting Information may be found in the online version of this article.

Clinical registration: The trial name—Examination regarding hypothalamus-pituitary-adrenal axis activity in mood disorder and post-traumatic stress disorder (PTSD) as determined by dexamethasone/corticotropin releasing hormone (DEX/CRH) test.

Contract grant sponsor: Japan Society for the Promotion of Science (JSPS); Contract grant numbers: 18790826 and 21791110; Contract grant sponsor: Mitsubishi Pharma Research Foundation.

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Received for publication 15 September 2010; Revised 27 March 2011; Accepted 18 April 2011

DOI: 10.1002/hbm.21354

Published online 3 December 2011 in Wiley Online Library (wileyonlinelibrary.com).

overprotection during childhood and adolescence and adulthood HPA axis hypoactivity, and between HPA axis hypoactivity and hippocampal GM volume reduction in healthy young adults, but no significant relationship was observed between any PBI scores and adulthood hippocampal GM volume. *Hum Brain Mapp 33:2211–2223, 2012.*

Key words: Hippocampus; parenting; dexamethasone; corticotropin-releasing hormone; magnetic resonance imaging

INTRODUCTION

The hypothalamus-pituitary-adrenal (HPA) axis activity, a major factor contributing to the enhancement or attenuation of cortisol release, has been considered as a potential marker of vulnerability to several stress-related diseases and neuropsychiatric disorders [Claes, 2004]. A reduced HPA axis activity, i.e., an attenuated cortisol response to acute psychosocial stress or neuroendocrine challenge, is associated with post-traumatic stress disorder (PTSD), chronic fatigue syndrome, or chronic burnout [Fries et al., 2005; Heim et al., 2000], whereas an elevated HPA axis activity, i.e., an excessive cortisol response to the abovementioned stimulations, is associated with recurrent depression or Alzheimer's disease [Aihara et al., 2007; Hatzinger et al., 1995]. Furthermore, recent human studies using the dexamethasone/corticotropin-releasing hormone (DEX/CRH) test [Heuser et al., 1994], which is considered as a highly sensitive probe of HPA axis activity, have also demonstrated that in adults without current neuropsychiatric disorders, a history of adverse parenting experiences during childhood and adolescence, such as physical, sexual, or emotional abuse, are significantly associated with an attenuated or an excessive cortisol response to DEX/CRH, suggesting that adverse parenting experiences during neurodevelopmental periods could leave long-lasting endocrinological scars expressed as HPA axis abnormalities in adulthood [Carpenter et al., 2009; Heim et al., 2008].

Recent human neuroimaging studies have suggested that adults with childhood maltreatment-related PTSD show a significant gray matter (GM) volume reduction in the hippocampus compared with controls [Bremner et al., 2003; Stein et al., 1997; Woon and Hedges, 2008]. The hippocampus, which is located in the medial temporal lobe and involved in learning and memory function, is believed to be modulated by the HPA axis through the effects of its two corticoid receptors (i.e., the mineralocorticoid receptor and the glucocorticoid receptor) and to provide negative feedback to the HPA axis [Conrad, 2008]. The neurotoxic effects of chronic HPA axis hyperactivity on the hippocampal structure have been well documented, e.g., cortisol hypersecretion in response to the DEX or DEX/CRH test correlates with hippocampal GM volume reduction in patients with depression and dementia [O'Brien et al., 1996], and hippocampal neuronal atrophy is found after high-dose cortisol administration in animals [Uno et al., 1994]. Therefore, it has been assumed in some studies that adverse parenting experiences during childhood and adolescence could induce chronic HPA axis hyperactivity, resulting in neurodevelopmental abnormalities, such as a hippocampal GM volume reduction in adulthood [Bremner et al., 2003; Stein et al., 1997]. Similarly, chronic HPA axis hypoactivity is suggested to induce a reduction of hippocampal GM volume in rats [Schubert et al., 2008]. Considering this animal study together with the abovementioned previous human research showing a significant association between a history of adverse parenting experiences and adulthood HPA axis hypoactivity, it might be hypothesized that adverse parenting experiences during childhood and adolescence could induce chronic HPA axis hypoactivity, resulting in an increased risk of hippocampal GM volume reduction with time. However, the associations among adverse parenting experiences during childhood and adolescence, HPA axis hypoactivity, and brain development, particularly hippocampal development, have been insufficiently investigated in humans.

Recently, Engert et al. [2010a,b] have carried out two notable studies regarding the associations among parenting experiences during childhood and adolescence, HPA axis activity, and hippocampal GM volume using the parental bonding instrument (PBI; a retrospective self-report scale to rate the attitudes of parents during the first 16 years) and cortisol response to psycosocial stress tasks. One study revealed that in young adults (aged, 18–30) without psychiatric disorders, those with a maternal medium-care score showed a significantly excessive cortisol response to a psychosocial stress task (i.e., the Trier Social Stress Test; TSST) [Kirschbaum et al., 1993] compared with those with maternal low- and high-care scores, suggesting that maternal low- and high-care scores, but not medium-care score during childhood and adolescence, are associated with HPA axis hypoactivity [Engert et al., 2010b]. Another study based on cortisol response to a psychosocial stress task (i.e., The Montreal Imaging Stress Task; MIST) [Dedovic et al., 2005] suggests a neurodevelopmental model, i.e., lower parental care score during childhood and adolescence induces an increasing adulthood HPA axis activity via hippocampal GM volume reduction in elderly adults (aged, 60–80) without psychiatric disorders

[Engert et al., 2010a]. These two significant studies provide beneficial evidence for associations among parenting experiences during childhood and adolescence, HPA axis activity, and hippocampal GM volume. However, these studies may have included subjects with HPA axis hyper-, normo- to hypoactivities as study samples because of the absence of an assessment of the subjects using neuroendocrine challenge tests, such as the DEX or DEX/CRH test. Considering the above-mentioned animal studies suggesting both HPA axis hypo- and hyperactivities are associated with hippocampal GM volume reduction or childhood parenting experience [Heim et al., 2001, 2008; Schubert et al., 2008; Uno et al., 1994], our understanding regarding associations of HPA axis hypoactivity with parenting experiences during childhood and adolescence and hippocampal GM development could be further improved by selecting individuals without HPA axis hyperactivity using neuroendocrine challenge tests and examining such individuals as study samples.

In this preliminary study, we used a cross-sectional design. Our subjects were healthy young adults with the following feature: no cortisol hypersecretion in response to the DEX (0.5 mg) test, no history of traumatic events, or no past or current conditions of significant medical illness or neuropsychiatric disorders. We aimed to examine the associations among PBI scores [Parker and Hadzi-Pavlovic, 1992; Parker et al., 1979], stimulated cortisol concentration in response to the DEX (0.5 mg)/CRH test, and GM volume focusing on the hippocampus by magnetic resonance imaging (MRI) with voxel-based morphometry (VBM) [Ashburner and Friston, 2000].

MATERIALS AND METHODS

Subjects

Forty-eight normal young adults, aged 18–35 years, were recruited from Gunma Prefecture, Japan, in accordance with the following exclusion criteria: history of a significant medical illness (e.g., neurological or endocrine diseases), a personality disorder, or a psychiatric illness (e.g., PTSD, schizophrenia, anxiety disorders, adjustment disorders, or mood disorders), history of a traumatic event (e.g., serious accident, physical, or sexual abuse), chronic alcoholism or substance abuse, or current chronic medication, in addition to parental divorce or history of a psychiatric illness within a participant's first-degree relatives. Furthermore, subjects were excluded from this study if they worked night shift. To exclude the subjects with past or current major mental disorders or personality disorders, the Structured Clinical Interview for DSM-IV Axis I Disorders [First et al., 1996] and that for Axis II Disorders [First et al., 1997] were used. Then, we excluded subjects with a possible HPA axis hyperactivity on the basis of their plasma cortisol concentration at first blood sampling (1400 h; basal cortisol concentration) in the DEX/CRH test, the details of which are shown in DEX/CRH Test Procedure. By this exclusion process, based on basal cortisol concentration, 8 of the 48 initial subjects were excluded from this study.

Finally, 40 subjects, aged 18–35 years (mean, 27.2 ± 5.2; 20 females), were enrolled in this study. All the 40 subjects were free of any medications for at least one month. Two subjects who smoked cigarettes were included in the study. In all the subjects, parental household income per year during a participant's childhood and adolescence was more than 5,000,000 yen (~$ 50,000), which is above the mean household income in Japan, as reported by the Japan Ministry of Health (http://www.mhlw.go.jp/toukei/itiran/dl/g02.pdf).

All the subjects enrolled in this study were right-handed as assessed using the Edinburgh Handedness Inventory [Oldfield, 1971]. All the subjects provided their written informed consent. The study protocol was approved by the Ethics Committee of Gunma University. Supporting Information Tables Ia,b and IIa,b show the demographic characteristics of parental low- and high-PBI-score groups, or parental low-, medium-, and high-PBI-score groups in this study subjects.

Experimental Procedure

On the first day of this examination and the following day, 48 subjects underwent the DEX/CRH test. Within one month after the DEX/CRH test, 40 subjects without cortisol hypersecretion in response to DEX (0.5 mg) (see DEX/CRH Test Procedure) filled out self-report questionnaires for psychological measurements including PBI and underwent MRI. On the same day, considering that the hippocampus is closely associated with cognitive functions [Conrad, 2008], the memory and attention function of the subjects were assessed using the Cambridge Neuropsychological Test Automated Battery (CANTAB) with a computer [Morris et al., 1987].

Psychological Measurements

PBI

The perceived parental rearing styles were assessed using the Japanese version of PBI. PBI is a self-report scale with 25 items to rate paternal or maternal attitude during the first 16 years, and has four items comprising care (range, 0–36 points) and overprotection (range, 0–39 points) factors, i.e., paternal care, maternal care, paternal overprotection, and maternal overprotection, the cut-off points of which are <24, < 27, < 12.5, and <13.5, respectively [Parker and Hadzi-Pavlovic, 1992; Parker et al., 1979]. The care factor has one pole defined by care and affection in the parent–child relationship and the other defined by indifference and rejection. The overprotection factor has one pole defined by control, overprotection, and intrusion and the other defined by encouragement of independence and autonomy. Furthermore, the overprotection factor has been reported to be further divided into two different subscales, i.e., score for denial of psychological autonomy (range, 0–21 points) and that for encouragement of behavioral freedom (range, 0–18 points) [Murphy et al., 1997].

Harvard trauma questionnaire (HTQ)

Furthermore, HTQ was used for the screening for PTSD, which is a reliable, validated, culturally sensitive instrument for measuring trauma and PTSD [Mollica et al., 1996]. The standard cut-off item score of 2.0 or higher was used to indicate a probable PTSD diagnosis [Mollica et al., 2001].

Zung self-rating depression scale (SDS)

For evaluation of depressive symptoms, all the subjects completed a questionnaire corresponding to the depression scale taken from SDS, which is a widely used inventory that consists of 20 items on a four-point scale, with a lower score representing a more favorable psychological state [Zung, 1965].

Japanese version of national adult reading test

The Japanese version of the National Adult Reading Test (JNART) was then used to estimate premorbid IQs [Matsuoka et al., 2006; Nelson, 1982].

Parental socioeconomic status (SES)

The subjects' SES and parental SES were assessed using the Hollingshead scale [Hollingshead, 1965].

Assessment of Cognitive Functional

CANTAB, which consists of neuropsychological tests using a touch screen portable computer, was administered to all the subjects for the assessment of cognitive function (the Cambridge Cognition website: http://www.cantab.-com/camcog/default.asp) [Morris et al., 1987]. Three tests of CANTAB were used in this study as follows: (1) Pattern recognition memory (PRM) is a test of visual recognition memory in a two-choice forced discrimination paradigm. The subject is presented with a series of 12 visual patterns, one at a time, at the centre of the screen. These patterns are designed such that they cannot easily be given verbal labels. In the recognition phase, the subject is required to choose between a pattern he/she has already seen and a novel pattern. In this phase, the test patterns are presented in the reverse order to the original order of presentation. (2) Spatial recognition memory (SRM) tests visual spatial memory in a two-choice forced discrimination paradigm. The subject is presented with a white square, which appears in sequence at five different locations on the screen. In the recognition phase, the subject sees a series of five pairs of squares, one of which is in a place previously seen in the presentation phase. The other square is in a location not seen in the presentation phase. (3) Rapid visual information processing (RVIP) is a visual continuous performance task, using digits instead of letters. A white box appears in the centre of the computer screen, inside which digits, from 2 to 9, appear in a pseudorandom order, at a rate of 100 digits per minute. Subjects are instructed to detect target sequences of digits (for example, 2-4-6, 3-5-7, 4-6-8) and to register responses using the press pad.

DEX/CRH Test Procedure

We modified the original method of Holsboer et al. [1995] as follows. A low dose of DEX (0.5 mg; Japanese brand name, "Dekadoron"; produced by Merck & Co., Inc., NJ) was administered orally at 2300 h, and at approximately 1330 h the following day each patient was instructed to lie in a supine position and a heparinized catheter was inserted into a cubital vein. At 1400 h, the first blood sample was drawn through the intravenous catheter, after which 100 μg of human CRH (Japanese brand name, "Mitsubishi"; produced by Mitsubishi Tanabe Pharma Corporation., Inc., Osaka, Japan) was administered intravenously instead of by CRH injection at 1500 h, as in previous studies [Heuser et al., 1994; Holsboer et al. 1995]. Blood samples were drawn again through the intravenous catheter at 1330 h, 1345 h, 1500 h, and 1515 h. Blood samples were immediately centrifuged and stored at −80°C. Plasma cortisol and adrenocorticotropic hormone (ACTH) concentrations were measured by radioimmunoassay at Mitsubishi Chemical Medience Corporation, Tokyo, Japan.

The results were evaluated in accordance with the method of Holsboer et al. [1995]. "Basal cortisol" and "basal ACTH" concentrations were defined as the plasma cortisol and ACTH concentrations at 1400 h of blood collection. After the area under the time course curve (AUC) was calculated by trapezoidal integration. "AUC_{net} cortisol" or "AUC_{net} ACTH" (corrected baseline of plasma cortisol or ACTH concentration, respectively) was computed as a measure of cortisol response to CRH injection. Thus, basal cortisol concentration (or basal ACTH) reflects the suppressive effect of DEX (0.5 mg) administered the day before, whereas AUC_{net} cortisol (or AUC_{net} ACTH) reflects the additional effects of CRH injection.

In this study, subjects with basal cortisol concentration higher than 4 μg/100 ml were excluded in accordance with the cut-off value that indicates nonsuppression of response to DEX (0.5 mg), which is considered to indicate HPA axis hyperactivity in the Japanese population [Matsunaga and Sarai, 2000].

MRI Acquisition

Brain MRI was performed using a Siemens 1.5-T Magnetom Symphony (Siemens, Erlangen, Germany). A three-dimensional gradient-echo sequence (fast low-angle shot, FLASH) yielding 160–192 contiguous slices of 1.0 mm thickness in the axial plane was used for volume analysis. This sequence provided high-resolution T1-weighted images with good contrast between GM and the white matter (WM). Imaging parameters were as follows: echo time = 5 msec; repetition time = 24 msec; flip angle = 40°; field of view = 256 mm; matrix size = 256 × 256; voxel size = 1 × 1 × 1 mm^3.

Image Analysis and Statistical Analyses

For voxel-based morphometry (VBM) [Ashburner and Friston, 2000], T1-weighted volumetric images were analyzed using SPM5 (Wellcome Department of Cognitive Neurology, London, UK) implemented in Matlab 2008a (MathWorks, Natick, MA, USA) to carry out VBM5.1 (http://dbm.neuro.uni-jena.de/vbm/download) using default parameters (DCT cutoff = 25 mm; nonlinear regularization = 1, 16 iterations). Each image was inspected for reconstruction artifacts. The VBM5.1 method combines spatial normalization, segmentation, and volumetric modulation. Each image was segmented into GM, WM, and cerebrospinal fluid using the Hidden Markov Random Field (HMRF) model, normalized to the International Consortium for Brain Mapping (ICBM) 152 template (Montreal Neurological Institute; MNI) (nonlinear transformation), and modulated with preservation of the total amount of GM. GM image segments were inspected for segmentation artifacts, then smoothed using an isotropic Gaussian kernel of 12 mm full width at half maximum (FWHM) [Mechelli et al., 2005]. An absolute threshold mask of 0.10 was used to avoid possible edge effects around the border between GM and WM. The significance level was set at $P < 0.05$ corrected for multiple comparisons at the cluster level and a familywise error rate of $P < 0.05$ at the voxel level (FWER-corrected $P < 0.05$) with adjustments for age, gender, and total GM volume.

Moreover, we performed region-of-interest (ROI) analysis by small volume correction to investigate the correlation between PBI scores or results of the DEX/CRH test and regional GM volume of the bilateral hippocampi by automated anatomical labeling (AAL) of the Wake Forest University (WFU) Pickatlas [Maldjian et al., 2003, 2004; Tzourio-Mazoyer et al., 2002], which provided an atlas-based method of generating ROIs (Fig. 2A). Furthermore, to determine total hippocampal GM volume in each subject, the mean signal intensities on T1-weighted images were extracted from the bilateral hippocampi for each subject using the MarsBar toolbox (http://marsbar.sourceforge.net) [Brett et al., 2002]. Total hippocampal GM volume, including the entire GM volume in the bilateral hippocampi was determined from the mean signal intensities on T1-weighted images within the bilateral hippocampi.

Statistical Analysis

Spearman's rho correlation and partial rank correlation with adjustments for confounding factors (i.e., age and gender, or age, gender, and total GM volume) were carried out to assess relationships among demographic characteristics, psychological and cognitive parameters, results of the DEX/CRH test, and total hippocampal GM volume. Student's t-test was used to assess gender differences. One-way analysis of variance (ANOVA) and analysis of covariance with adjustments for confounding factors were used to compare AUC_{net} cortisol or total hippocampal GM volume between low- and high-PBI score classified on the basis of the cut-off score of each PBI item (i.e., paternal care, paternal overprotection, maternal care or maternal overprotection) [Parker and Hadzi-Pavlovic, 1992; Parker et al., 1979], using SPSS for Windows ver. 12 (SPSS Japan Inc., Tokyo, Japan). Finally, considering a previous PBI study by Engert et al. [2010b] revealing that maternal medium-care score group shows a significantly excessive cortisol response to a psychosocial stress task compared with the maternal low- and high-care score groups, we divided our subjects into three groups (low-, medium-, and high-PBI score groups) on the basis of the ascending order of score of each PBI item, and compared the three groups, by one-way ANOVA with Bonferroni.

RESULTS

Table I shows the demographic characteristics, psychological measures, ACTH and cortisol levels, and hippocampal volumes of the study subjects. No significant gender differences were observed in basal cortisol concentration, AUC_{net} cortisol, and total hippocampal volume. The HTQ scores of all the subjects were below 2.0, which is the standard cut-off score indicating a probable PTSD diagnosis [Mollica et al., 2001].

Spearman's rho correlation showed that neither basal cortisol concentration nor AUC_{net} cortisol correlated with age, education years, SES score, parental SES score, JNART score, depressive symptom score, or scores of cognitive function tests (i.e., PRM, SRM, and RVIP). Moreover, neither basal ACTH concentration nor AUC_{net} ACTH correlated with age, education years, SES score, parental SES score, JNART score, depressive symptom score, or scores of cognitive function tests. AUC_{net} ACTH significantly correlated with AUC_{net} cortisol ($r = 0.634$, $P < 0.01$), and this significance remained after adjustments for age and gender ($r = 0.658$, $P < 0.01$). All PBI scores (i.e., parental care and overprotection scores) and all parental overprotection subscale scores (i.e., score for parental denial of psychological autonomy and paternal encouragement of behavioral freedom) did not correlate with basal ACTH concentration, AUC_{net} ACTH, or basal cortisol concentration. On the other hand, paternal and maternal overprotection scores significantly negatively correlated with AUC_{net} cortisol ($r = -0.356$, $P < 0.05$ and $r = -0.366$, $P < 0.05$, respectively). The significance of these correlations remained after adjustments for age and gender ($r = -0.339$, $P < 0.05$ and $r = -0.353$, $P < 0.05$, respectively). Neither paternal nor maternal care scores significantly correlated with AUC_{net}

TABLE I. Demographic characteristics, psychological measures, ACTH and cortisol levels, and hippocampal volumes of demographic characteristics of study subjects

	Male	Female
Number	20	20
Age (y)	28.4 ± 4.8	25.9 ± 5.3
Education (y)	15.9 ± 1.5	14.6 ± 1.9
SES score (point)	3.4 ± 0.9	3.6 ± 0.7
Parental SES score (point)	2.8 ± 1.6	3.0 ± 1.7
JART—predicted full-scale IQ	103.0 ± 8.3	107.0 ± 9.5
CANTAB (Z-score)		
Pattern recognition memory*	0.01 ± 0.59	0.36 ± 0.40
Spatial recognition memory	0.54 ± 0.65	0.42 ± 1.23
Rapid visual information processing	0.87 ± 0.77	0.82 ± 0.94
Depressive symptom score (point)	35.1 ± 7.8	37.1 ± 8.9
Parental bonding instrument (point)		
Paternal care	23.2 ± 6.8	24.2 ± 4.6
Paternal overprotection	10.6 ± 6.9	10.6 ± 4.9
Maternal care	26.4 ± 5.1	26.6 ± 5.4
Maternal overprotection	10.3 ± 5.9	10.2 ± 6.7
Dexamethasone (0.5mg)/CRH test		
Basal ACTH (ng/ml)	5.6 ± 3.9	4.6 ± 2.2
AUC_{net} ACTH (ng/ml min)	1029.1 ± 483.1	953.9 ± 523.2
Basal cortisol (μg/100ml)	1.6 ± 1.1	1.6 ± 1.2
AUC_{net} cortisol (μg/100ml min)	304.8 ± 179.4	338.8 ± 218.3
Brain tissue to intracranial volume ratio		
Gray matter/intracranial volume	0.457 ± 0.030	0.463 ± 0.025
White matter/intracranial volume	0.315 ± 0.024	0.305 ± 0.028
Cerebrospinal fluid/intracranial volume	0.228 ± 0.031	0.231 ± 0.042
Average gray matter density in bilateral hippocampi	0.487 ± 0.018	0.501 ± 0.021

Abbreviations: SES, socioeconomic status; JART, the Japanese version of the National Adult Reading Test; AUC_{net} cortisol, corrected baseline of plasma cortisol concentration, after the area under the time course curve (AUC) was calculated by trapezoidal integration; CANTAB, the Cambridge Neuropsychological Test Automated Battery, which is expressed as Z-score calculated from the internal normative database of CANTAB, involving 3,000 healthy volunteers. Mean ± SD.
*$P < 0.05$ (Student's *t*-test).

cortisol (Fig. 1). Moreover, all parental overprotection subscale scores did not significantly correlate with AUC_{net} cortisol (Supporting Information Fig. 1). Total hippocampal GM volume significantly positively correlated with AUC_{net} cortisol ($r = 0.402$, $P < 0.05$), and the significance of this correlation remained after adjustments for age, gender, and total GM volume ($r = 0.339$, $P < 0.05$) (Fig. 2C), whereas no significant correlation was observed between total hippocampal GM volume and basal ACTH concentration, AUC_{net} ACTH, or basal cortisol concentration. Total hippocampal GM volume did not significantly correlate with the subjects' and parental SES scores, education years, JNART scores, depressive symptom score, and all PBI scores and parental overprotection subscale scores. Total hippocampal GM volume significantly negatively correlated with maternal overprotection scores ($r = -0.400$, $P < 0.05$) and significantly positively correlated with maternal care score ($r = 0.334$, $P < 0.05$, respectively), but these significances did not remain after adjustments for age, gender, and total GM volume ($r = -0.194$, NS and $r = 0.306$, NS, respectively). Furthermore, total hippocampal GM volume significantly negatively correlated with the number of incorrect answers in PRM of cognitive function tests ($r = -0.340$, $P < 0.05$), but this significance did not remain after adjustments for age, gender, and total GM volume ($r = -0.165$, NS). Total hippocampal GM volume did not significantly correlate with SRM and RVIP scores in cognitive function tests.

Correlation of PBI Scores (i.e., Care and Overprotection Scores) or AUC_{net} Cortisol With Regional GM Volume in Whole Brain Determined by VBM

When we estimated the regional GM volume of areas within the entire brain that statistically significantly correlated with each PBI score (i.e., paternal care, paternal overprotection, maternal care, or maternal overprotection score), no significant positive or negative correlation was found in any GM area (FWER-corrected $P > 0.05$). Similarly, when we estimated the regional GM volume of areas within the entire brain that were statistically significantly associated with AUC_{net} cortisol, no significant positive or

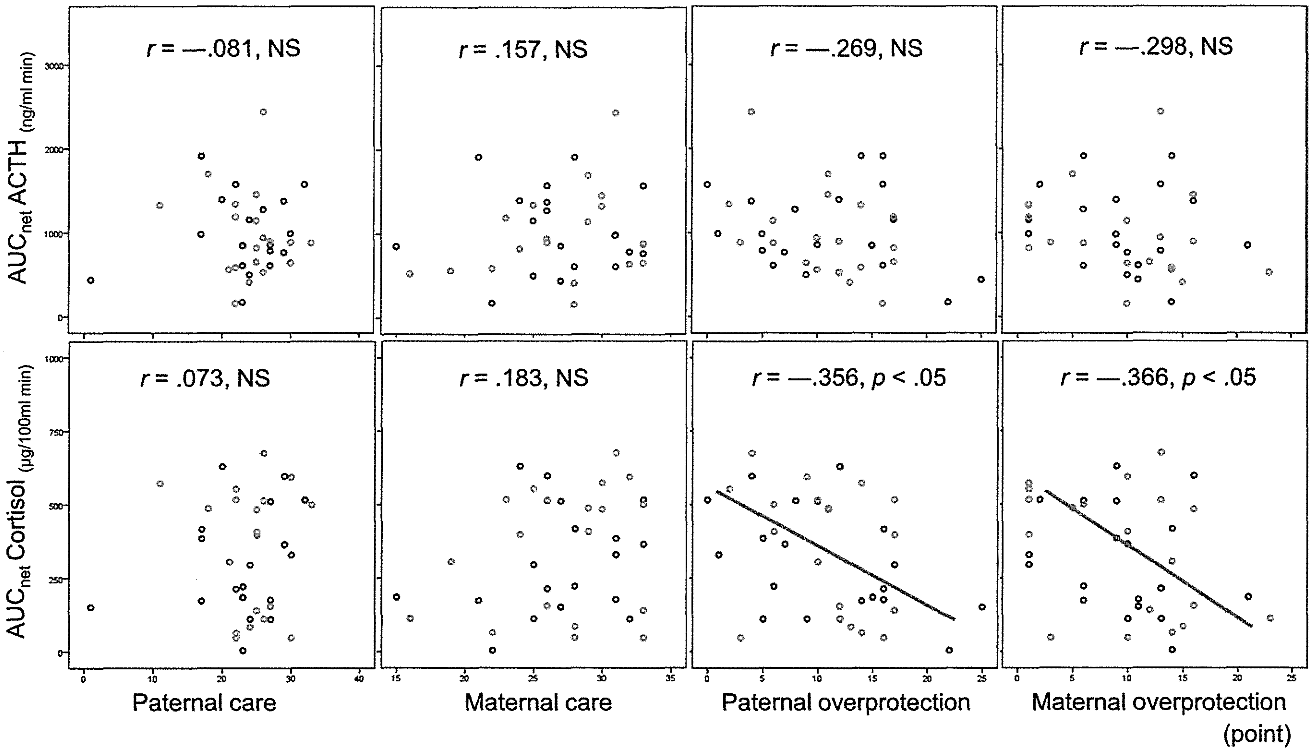

Figure 1.
Associations between scores of PBI (i.e., care and overprotection) and AUC_{net} cortisol, or AUC_{net} ACTH. Blue circles indicate male subjects and green circles indicate female subjects. Spearman's rho correlation, $P < 0.05$.

negative correlation was found in any GM area (FWER-corrected $P > 0.05$).

Small-Volume Correction to Estimate Correlation of PBI Scores (i.e., Care and Overprotection Scores) or AUC_{net} Cortisol With Regional GM Volume Within Bilateral Hippocampi Determined by VBM With AAL of WFU Pickatlas

PBI scores and regional GM volume focusing on bilateral hippocampi

When we estimated the regional GM volume of areas focusing on the bilateral hippocampi that were statistically significantly associated with each PBI score, no significant positive or negative correlation was found in any GM area within the bilateral hippocampi (FWER-corrected $P > 0.05$).

AUC_{net} cortisol and regional GM volume focusing on bilateral hippocampi

An ROI analysis focusing on the bilateral hippocampi showed that AUC_{net} cortisol positively correlated with GM volume in the left hippocampus (FWER-corrected $P < 0.05$), after adjustments for age, gender, and total GM volume (Fig. 2B, Table II). On the other hand, no significant negative correlation between AUC_{net} cortisol and GM area within the bilateral hippocampi was found (FWER-corrected $P > 0.05$).

Estimation of Differences in AUC_{net} Cortisol and Total Hippocampal GM Volume between Parental Low- and High-PBI-Score Groups (i.e., Care and Overprotection Scores)

AUC_{net} cortisol

One-way ANOVA showed no significant association in AUC_{net} cortisol between the paternal low-care-score group ($n = 17$) and the paternal high-care-score group (I = 23) ($F = 0.323$, $P = 0.573$). Moreover, no significant association in AUC_{net} cortisol was observed between the maternal low-care-score group ($n = 19$) and the maternal high-care-score group ($n = 21$) ($F = 0.560$, $P = 0.459$). The paternal low-overprotection-score group ($n = 24$) has a significantly higher AUC_{net} cortisol than the paternal high-overprotection-score group ($n = 16$) ($F = 7.108$, $P = 0.011$), and this significance remained after adjustments for age and

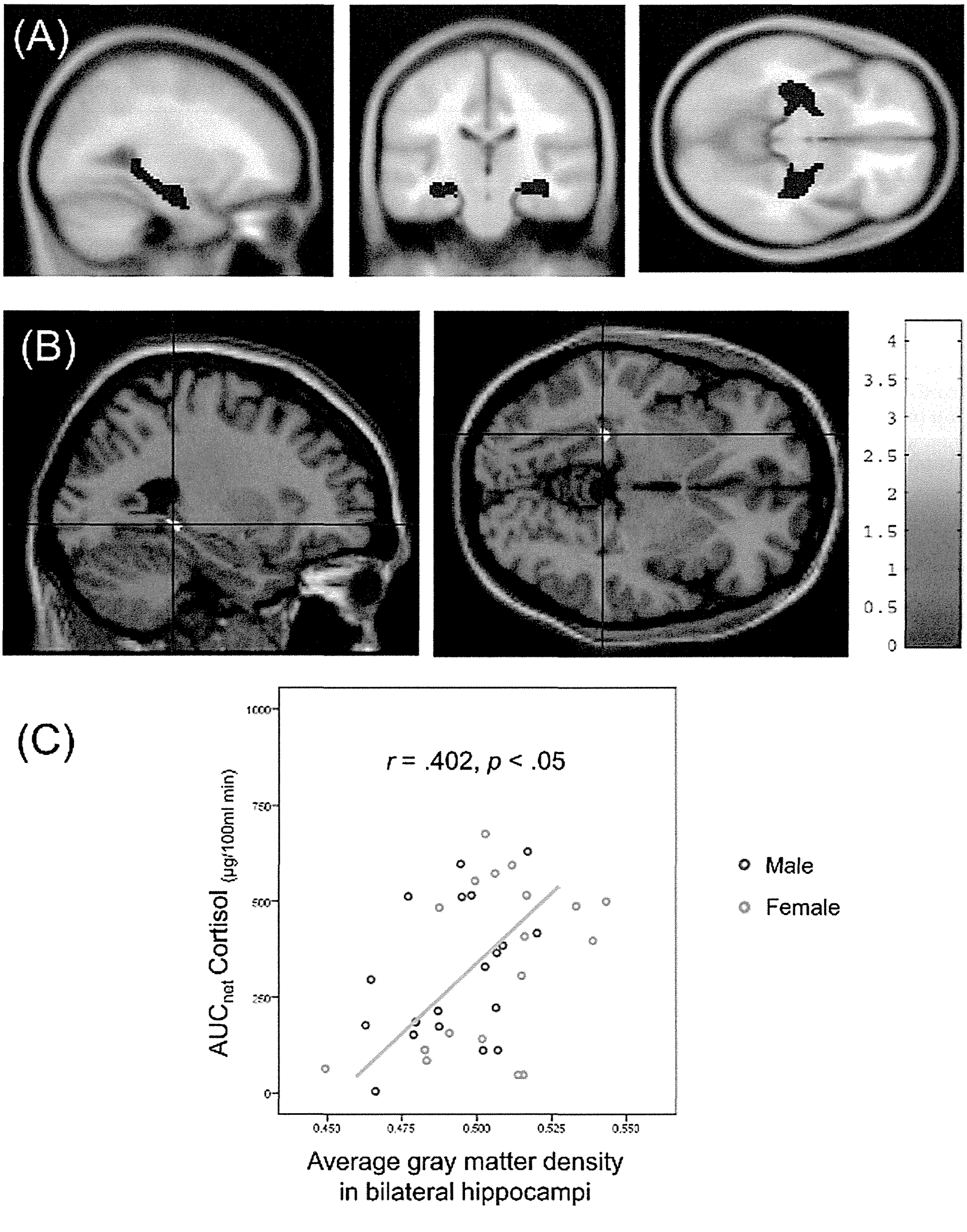

Figure 2.

Panel (A) shows the brain region including the bilateral hippocampi (blue area), masked by automated anatomical labeling (AAL) of the Wake Forest University (WFU) Pickatlas, which provided an atlas-based method of generating ROIs. Panel (B) shows the brain region that significantly positively correlated with AUC_{net} cortisol, as determined by ROI analysis focusing on the hippocampus. The blue lines indicate the left tail in the hippocampus. The statistical threshold was set at $P < 0.05$ corrected for multiple comparisons at the cluster level and a familywise error rate of $P < 0.05$ at the voxel level (FWER-corrected $P < 0.05$) with adjustments for age, gender, and total GM volume. Panel (C) shows the association between AUC_{net} cortisol and total hippocampal GM volume, as determined by the mean signal intensities on T1-weighted images within the bilateral hippocampi. Blue circles indicate male subjects and green circles indicate female subjects. Spearman's rho correlation, $P < 0.05$.

TABLE II. Brain region showing significant positive correlation between AUC_{net} cortisol and average gray matter density in bilateral hippocampi after adjustments for age, gender, and total gray matter volume

	Cluster level		Peak coordinates[a]			Voxel level	
	Corrected *P*	*k*	*x*	*y*	*z*	*t*	FWER-corrected *p*
L hippocampus	0.025	137	−25	−38	−4	4.31	0.018

[a] *x, y, z,* are the stereotaxic coordinates, as given in Montreal Neurological Institute Atlas.
L, left. The significance level was set at $P < 0.05$ corrected for multiple comparisons at the cluster level, and $P < 0.05$ familywise error rate (FWER-corrected) at the voxel level.

gender ($F = 5.794$, $P = 0.021$). Also, the maternal low-overprotection-score group ($n = 28$) has a significantly higher AUC_{net} cortisol than the maternal high-overprotection-score group ($n = 12$) ($F = 4.384$, $P = 0.043$), and this significance remained after adjustments for age and gender ($F = 4.277$, $= 0.046$).

Total hippocampal GM volume

One-way ANOVA showed no significant association in total hippocampal GM volume between the paternal low-care-score and paternal high-care-score groups ($F = 0.035$, $P = 0.852$). Also, no significant association in total hippocampal GM volume was observed between the maternal low-care-score and maternal high-care-score groups ($F = 3.858$, $P = 0.057$). The paternal low-overprotection-score group showed a significantly greater total hippocampal GM volume than the paternal high-overprotection-score group ($F = 5.494$, $P = 0.024$), but this significance did not remain after adjustments for age and gender ($F = 3.194$, $P = 0.083$). Also, the maternal low-overprotection-score group has a significantly greater total hippocampal GM volume than maternal high-overprotection-score group ($F = 7.694$, $P = 0.009$), but this significance did not remain after adjustments for age and gender ($F = 2.834$, $P = 0.101$) (see Supporting Information Table 1a,b).

Estimation of Differences in AUC_{net} Cortisol or Total Hippocampal GM Volume Among Parental Low-, Medium-, and High-PBI-Score Groups (i.e., Care and Overprotection Scores)

One-way ANOVA with Bonferroni showed no significant associations in AUC_{net} cortisol among low-, medium-, and high-score groups for each PBI items, i.e., paternal care (low: $n = 13$; range, 1–22 points; medium: $n = 16$; range, 23–26 points; and high: $n = 11$; range, 27–33 points), paternal overprotection (low: $n = 13$; range, 0–8 points; medium: $n = 12$; range, 9–13 points; and high: $n = 15$; range, 14–25 points), maternal care (low: $n = 14$; range, 15– 25 points; medium: $n = 13$: range, 26–29 points; and high: $n = 13$; range, 30–33 points), or maternal overprotection (low: $n = 13$; range, 1–6 points; medium: $n = 15$; range, 9–13 points; and high: $n = 12$; range, 14–23 points). Also, no significant associations in total hippocampal volume were observed among the low-, medium- and high-score-groups for each PBI item (Supporting Information Table 2a,b).

DISCUSSION

From the results of the correlation analyses and comparisons between the low- and high-PBI-score groups in this study, a significant negative association was found between parental overprotection scores and AUC_{net} cortisol, suggesting that parental overprotection during the first 16 years increases the risk of dampening of cortisol reactivity, i.e., HPA axis hypoactivity, in adulthood. On the other hand, parental care scores did not correlate with AUC_{net} cortisol. A significant positive correlation between cortisol response to DEX/CRH and GM volume in the hippocampus was observed (Fig. 2B,C), suggesting that HPA axis hypoactivity is associated with the hippocampal GM volume reduction, which is consistent with previous animal studies that demonstrated that chronic HPA axis hypoactivity after adrenalectomy contributes to the GM volume reduction of the hippocampus [Fries et al., 2005; Schubert et al., 2008]. However, parental care and overprotection scores were not significantly associated with total or regional hippocampal GM volume. In addition, no significant difference was observed in AUC_{net} cortisol or total hippocampal GM volume between parental low-, medium-, and high-PBI-score groups.

As far as we know, there has been no study describing an association between PBI scores and cortisol response to DEX/CRH test. In previous research on cortisol response to neuroendocrine challenge, association between HPA axis activity and parenting experiences during childhood and adolescence was studied previously in nondepressed human adults with a history of early-life stress, using original interview, structured interview (i.e., the Early Trauma Inventory), or childhood trauma questionnaire (CTQ; a self-report scale containing items of emotional, physical, and sexual abuses)] to measure parenting experiences during childhood and adolescence [Carpenter et al., 2009; Heim et al., 2001, 2008], but the results of such studies are inconsistent. Heim et al. [2001] described that childhood physical or sexual abuse is associated with lower basal cortisol and stimulated plasma cortisol concentrations in response to iv CRH and ACTH challenge tests. Another