NeuroImage: Clinical 12 (2016) 600–606

Contents lists available at ScienceDirect

NeuroImage: Clinical

journal homepage: www.elsevier.com/locate/ynicl

Low putamen activity associated with poor reward sensitivity in childhood chronic fatigue syndrome

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ARTICLE INFO

Article history:
Received 15 July 2016
Received in revised form 22 September 2016
Accepted 23 September 2016
Available online 26 September 2016

Keywords:
Childhood chronic fatigue syndrome
Dopamine
fMRI
Motivation
Putamen
Reward sensitivity

ABSTRACT

Motivational signals influence a wide variety of cognitive processes and components of behavioral performance. Cognitive dysfunction in patients with childhood chronic fatigue syndrome (CCFS) may be closely associated with a low motivation to learn induced by impaired neural reward processing. However, the extent to which reward processing is impaired in CCFS patients is unclear. The aim of the present functional magnetic resonance imaging (fMRI) study was to determine whether brain activity in regions related to reward sensitivity is impaired in CCFS patients. fMRI data were collected from 13 CCFS patients (mean age, 13.6 ± 1.0 years) and 13 healthy children and adolescents (HCA) (mean age, 13.7 ± 1.3 years) performing a monetary reward task. Neural activity in high- and low-monetary-reward conditions was compared between CCFS and HCA groups. Severity of fatigue and the reward obtained from learning in daily life were evaluated by questionnaires. Activity of the putamen was lower in the CCFS group than in the HCA group in the low-reward condition, but not in the high-reward condition. Activity of the putamen in the low-reward condition in CCFS patients was negatively and positively correlated with severity of fatigue and the reward from learning in daily life, respectively. We previously revealed that motivation to learn was correlated with striatal activity, particularly the neural activity in the putamen. This suggests that in CCFS patients low putamen activity, associated with altered dopaminergic function, decreases reward sensitivity and lowers motivation to learn.

1. Introduction

Fatigue causes difficulty initiating or sustaining voluntary activities (Chaudhuri and Behan, 2004a). Fatigued children and adolescents and patients with childhood chronic fatigue syndrome (CCFS), which is characterized by profound and disabling fatigue for at least 3 months (Jason et al., 2006), show poor performance on cognitive tasks related to memory and attention (Tomoda et al., 2007; Haig-Ferguson et al., 2009; Kawatani et al., 2011; Mizuno and Watanabe, 2013a; Mizuno et al., 2015a). In addition to cognitive dysfunction, CCFS patients also exhibit severe emotional dysfunction such as reduced motivation to learn (Miike and Bell, 2008). Motivational signals influence a wide variety of cognitive processes and components of behavioral performance (Botvinick and Braver, 2015); therefore, cognitive dysfunction in CCFS patients may be closely associated with a low motivation to learn which derives from impaired neural reward processing.

Using functional magnetic resonance imaging (fMRI), we previously revealed that motivation to learn was correlated with striatal activity, particularly the neural activity in the putamen (Mizuno et al., 2008). An fMRI study of adult patients with chronic fatigue syndrome (CFS)

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http://dx.doi.org/10.1016/j.nicl.2016.09.016

showed impaired striatal activity during perception of monetary reward (Miller et al., 2014). However, it is unclear whether neural reward processing is impaired in CCFS patients.

Children and adolescents with attention deficit hyperactivity disorders (ADHD) have impaired reward processing. They require stronger rewards to modify their behavior and learn faster when using direct reinforcement (Kollins et al., 1998). This suggests that neural responses in ADHD patients are decreased during low-value reward conditions. Our recent fMRI study revealed that children and adolescents with ADHD had decreased responses to reward (decreased reward sensitivity), associated with abnormally low activity in the striatum and thalamus, from small rewards (Mizuno et al., 2013b). After 3 months treatment with a dopaminergic agent (osmotic release oral system-methylphenidate), the striatal and thalamic activities improved to the same level as observed in healthy controls (Mizuno et al., 2013b), suggesting that the decrease in reward sensitivity involves decreased dopaminergic activity in the striatum and thalamus, which are regions rich in dopaminergic neurons. In adults with CFS, methylphenidate treatment for 4 weeks reduced the severity of fatigue (Blockmans et al., 2006), suggesting that neural reward processing based on dopaminergic function was also impaired in these patients. Therefore, in this study we focused on dopaminergic dysfunction in CCFS patients. The aim of the present fMRI study was to determine brain activity in regions related to reward sensitivity in CCFS patients.

2. Materials and methods

2.1. Participants

Healthy children and adolescents (HCA) and CCFS patients, all of whom fulfilled the diagnostic criteria for CCFS (Jason et al., 2006), were recruited from Kumamoto University Hospital. CCFS patients with a diagnosis of neurological illness, migraine, obstructive sleep apnea, below average intelligence, or severe psychopathology were excluded from the study. Serious psychopathology was defined as referral to at least one pediatric psychiatrist if the patient presented with indicative symptoms. No patients or healthy participants had any history of Diagnostic and Statistical Manual of Mental Disorders Fourth Edition, Text Revision (DSM-IVTR) Axis I Disorder (based on Structured Clinical Interview for DSM-IV Axis I Disorders), drug abuse, head injury, or fetal drug exposure that may have influenced brain development.

Fourteen patients with CCFS and 13 HCA participated in the fMRI experiments. All participants were right-handed according to the Edinburgh handedness inventory (Oldfield, 1971) and scored >80 on the full-scale intelligence quotient derived from the Wechsler Intelligence Scale for Children (Wechsler, 1991). All patients with CCFS were undergoing treatments such as medication with antidepressants, and all medications were discontinued for four weeks before the fMRI experiments. One patient was excluded from analysis because the quality of the MRI data was low due to noise caused by dental corrective devices. Therefore, we analyzed data obtained from 13 CCFS patients and 13 HCA. The physical and neuropsychological characteristics of the participants are shown in Table 1. Age, body mass index, and full-scale intelligence quotient score were well matched between the CCFS and HCA groups.

The protocol was approved by the Ethics Committee of Kumamoto University, and all participants and their parents gave written informed consent for participation in the study. The experiments were undertaken in compliance with national legislation and the Code of Ethical Principles for Medical Research Involving Human Subjects of the World Medical Association (Declaration of Helsinki).

2.2. Questionnaires

The severity of fatigue was evaluated using the Chalder Fatigue Scale (Chalder et al., 1993; Tanaka et al., 2008). This fatigue scale consists of 11 items, each scored on a four-point scale (range, 0–3) that allows the following responses: 0 = less than usual; 1 = no more than usual; 2 = more than usual; and 3 = much more than usual during the past several weeks. The total score for the 11-item fatigue scale ranges from 0 to 33, with higher scores indicating greater fatigue.

Table 1
Physical and psychological characteristics.

	HCA	CCFS	*P* value
Sex (female/male)	9/4	6/7	0.428
Age (years)	13.7 ± 1.3	13.6 ± 1.0	0.862
BMI (kg/m^2)	19.8 ± 2.4	18.4 ± 2.3	0.141
Disease duration (months)	–	25.5 ± 25.4	–
FIQ score	100.0 ± 12.4	100.5 ± 9.6	0.903
Chalder FS score	8.8 ± 6.2	17.8 ± 6.2	0.001
LERI			
Effort score	4.5 ± 1.0	4.3 ± 0.9	0.671
Reward score	6.4 ± 1.1	5.5 ± 1.2	0.075
OC score	3.5 ± 0.5	3.5 ± 0.7	0.744
LERI ratio	0.96 ± 0.25	1.09 ± 0.34	0.268

HCA, Healthy children and adolescents; CCFS, childhood chronic fatigue syndrome; BMI, Body mass index; FIQ, Full scale intelligence quotient; Chalder FS, Chalder fatigue scale; LERI, Effort-reward imbalance for learning model questionnaire; OC, over commitment. Values are presented as number or mean ± SD. *P* values were obtained using Fisher's exact test or Student's *t*-test.

The balance between effort and reward was evaluated using the effort-reward imbalance for learning model questionnaire (LERI) (Fukuda et al., 2010). The LERI consists of 10 items (three items on effort for learning, four items on reward from learning, and three items on over commitment), each scored on a two-point scale (1, no or 2, yes) for learning in the past few weeks. Higher scores for effort for learning and reward from learning indicate greater degrees of effort and reward, respectively. The LERI ratio was calculated as follows: (effort-for-learning score × 4) / (reward-from-learning score × 4). Higher scores indicate a greater degree of effort than reward. The Chalder Fatigue Scale and LERI questionnaires were distributed to participants before the fMRI experiments.

2.3. Experimental paradigm for fMRI

fMRI studies of the neural substrates associated with reward sensitivity indicate that the activity response of brain regions involved in the reward system is associated with the magnitude of the reward (Izuma et al., 2008; Mizuno et al., 2013b, 2015b). The fMRI experimental design is shown in Fig. 1. In the monetary reward condition, participants performed a simple gambling task. This was a block-design version of the task used in the previous study (Mizuno et al., 2013b, 2015b). Participants were encouraged to try to earn as much money as possible and were told that one session would be randomly chosen at the end of the experiment and that their earnings in that session would be given to them. In each trial (3 s), participants were presented with three cards labeled "A", "B", and "C" and were asked to choose one card within 2 s by pressing a button with the right index, middle, or ring finger, which spatially corresponded to the location of the cards. Immediately after the button press, the chosen card was highlighted with a thick white border, and the outcome was displayed for 1 s. If the participants did not press any button within the choice period (2 s), the card they had chosen in the previous trial was automatically chosen, and its outcome was displayed.

When the letters on the cards were written in red, the trial was a monetary reward trial, in which each card was randomly associated with 0, 30, or 60 yen. Each condition consisted of eight trials (24 s). However, unknown to the participants, the total reward that they could earn in each condition was predetermined. In the high-monetary-reward (HMR) condition, in which they chose one card for each of 8 trials, they earned an average of 330 yen (range = 270–390 yen) which was higher than the expected value of 240 yen. In the low-

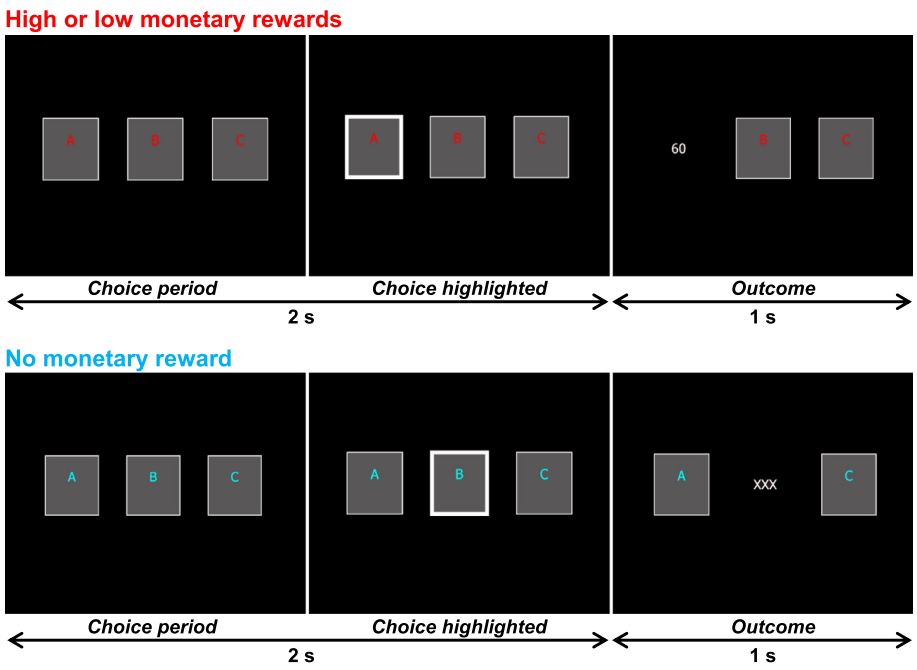

Fig. 1. Monetary reward task. Stimulus display sequence for the high- and low-monetary-reward trials (top) and the no-monetary-reward trial (bottom). In each trial, participants were asked to choose one card within 2 s. In each monetary reward trial, the outcome of the chosen card (0, 30, or 60 yen) was shown for 1 s. In each no-monetary reward trial, the outcome was always "×××", indicating no monetary reward. Each block consisted of eight monetary-reward or no-monetary-reward trials (24 s).

monetary-reward (LMR) condition, they earned an average of 150 yen (range = 90–210 yen), which is lower than the expected value. The participants knew that the expected value of the eight reward trials was 240 yen; however, they were not informed of the presence of the HMR and LMR conditions. They also participated in a no-monetary-reward (NMR) condition, indicated by blue letters, in which they chose one card, but the outcome presented was always "×××", indicating that there was no monetary reward. The NMR condition, or a rest condition of fixation with a blank screen (24 s), was always inserted between two reward conditions, so that the start and end of the reward manipulations could be clearly defined. For a half of the participants, the colors (red and blue) used for the monetary reward and NMR conditions were switched to control for differences in activity related to visual processing of colors.

All participants completed a practice task for 2 min before scanning to ensure that they understood the task. During the practice task we confirmed that all participants chose one card within the choice period (2 s) with 100% accuracy (moving average of eight trials). During scanning, participants performed four repeats of each of the four conditions HMR, LMR, NMR, and fixation rest (24 s per condition of 8 × 3 s trials) for a total of 6 min 24 s. In each session, the HMR and LMR conditions were ordered differently, and the order of the four sessions was counterbalanced across participants. All participants were paid a fixed amount for their participation at the end of the experiment.

2.4. fMRI acquisition and analysis

All images were obtained using a 3-T MR scanner (TRIO A Tim; Siemens, Erlangen, Germany) located at the Graduate School of Medical Sciences, Kumamoto University. For functional imaging, a series of 528 volumes (132 volumes per session) were acquired using interleaved T2-weighted, gradient echo, echo planar imaging (EPI) sequences. Each volume consisted of 44 transaxial slices that included the entire cerebrum and cerebellum, with a slice thickness of 3.0 mm [repetition time (TR), 3000 ms; echo time (TE), 30 ms; flip angle (FA), 90°; field of view (FOV), 192 mm; in-plane matrix size, 64 × 64 pixels, voxel dimensions, 3.0 × 3.0 × 3.0 mm; slice gap, 0 mm]. Comfortable foam padding was tightly placed around the participant's head to minimize head movement. To acquire a fine structural whole-brain image, magnetization-prepared rapid-acquisition gradient-echo (MP-RAGE) images were obtained [TR, 1900 ms; TE, 4.62 ms; flip angle, 15°; FOV, 256 mm; one slab; number of slices per slab, 176; voxel dimensions, 1.0 × 1.0 × 1.0 mm].

The first four volumes acquired in each MRI session were discarded due to unsteady magnetization, and the remaining 128 volumes per session were used for analyses. Data were analyzed using the Statistical Parametric Mapping 8 package (The Wellcome Trust Centre for Neuroimaging, London, UK; http://www.fil.ion.ucl.ac.uk/spm) implemented in MATLAB 7.13.0.564 (Mathworks, Natick, MA). All images in the EPI time series were realigned and a mean image was created. High-resolution whole-brain T1-weighted images were then co-registered with the mean image. This structural image was then normalized to the Montréal Neurological Institute (MNI) T1 image template (Evans et al., 1994), with the same parameters applied to all EPI images. The EPI images were spatially smoothed in three dimensions using an 8-mm full-width half-maximum Gaussian kernel.

Statistical analyses were performed at two levels. First, individual task-related activation was evaluated. The task performed was a simple gambling task, and was a block-design version of the task used in a previous study (Izuma et al., 2008; Mizuno et al., 2013b, 2015b). A block consisted of eight trials (8 trials × 3 s = 24 s) in each condition (i.e. HMR, LMR and NMR). Therefore, the duration of each event (one block) was 24 s. Each task condition was repeated four times in one session. We modeled three regressors (HMR, LMR, and NMR), which were convolved with a canonical hemodynamic response function to obtain the expected signal changes caused by the tasks. Regressors that were of no interest, such as the six realignment parameters that account for motion-related variance, were also included in the design model. The data were high-pass filtered with a cut-off period of 128 s to remove low-frequency signal drifts. An autoregressive model was used for whitening the residuals so as to meet the assumptions for application of a general linear model. The effect of each condition was evaluated with

a general linear model. The weighted sum of the parameters estimated in the individual analyses consisted of "contrast" images. Specifically, for each participant, the following first-level contrast images were generated: [HMR *minus* NMR] and [LMR *minus* NMR].

Second, the contrast images corresponding to each condition for each participant were used for group analyses with a random-effects model to obtain population inferences (Friston et al., 1999). A flexible factorial design, which can compare the activities of reward-level contrasts within [HMR *minus* NMR] and [LMR *minus* NMR], and between HCA and CCFS patients, was used. The resulting set of voxel values for each comparison constituted a statistical parametric map of *t* statistics [SPM(*t*)]. Significant signal changes for each contrast were assessed by means of *t* statistics on a voxel-by-voxel basis. Regions of interest for the caudate, putamen, and thalamus were defined based on the results of reward sensitivity analyses and the outcome of our previous study (Mizuno et al., 2013b, 2015b) and were constructed using the Wake Forest University Pick-Atlas (Maldjian et al., 2003) as one mask image. The threshold for the SPM(*t*) for group analyses was set at $P < 0.05$ with a family-wise error correction for multiple comparisons both at the voxel level and at the cluster level for clusters larger than five voxels (Mizuno et al., 2015b).

The effect of task condition (HMR, LMR, NMR) and study group (HCA, CCFS) on task performance (reaction time) was analyzed using a two-way analysis of variance. When statistically significant effects were found, intergroup differences were evaluated using Student's *t*-test. All *P* values were two-tailed, and *P* values < 0.05 were considered significant. These analyses were performed with the IBM SPSS 20.0 software package (SPSS Inc., Chicago, IL).

3. Results

3.1. Questionnaire results

The results for the questionnaires are summarized in Table 1. The Chalder Fatigue Scale score in the CCFS group was much higher than that in the HCA group. The LERI effort-for-learning score and overcommitment score were not different between the HCA and CCFS groups, but the LERI reward-from-learning score tended to be lower in the CCFS group than in the HCA group.

3.2. Behavioral results

The reaction times are summarized in Table 2. A two-way analysis of variance revealed no significant main effect of task condition [$F(2, 72) = 0.71$, $P = 0.497$] or study group [$F(1, 72) = 1.84$, $P = 0.180$] on reaction time, and no interaction between task condition and study group [$F(2, 72) = 0.25$, $P = 0.975$].

3.3. Imaging results

Imaging results for the HMR and LMR conditions (HMR or LMR *minus* NMR) are shown in Fig. 2. In the HMR condition, activation of the bilateral caudate, putamen, and thalamus was commonly observed in both the HCA group and the CCFS group. In the LMR condition, activation of the bilateral caudate and thalamus was commonly observed in both the HCA group and the CCFS group, but activation of the bilateral putamen was only observed in the HCA group. The subtraction contrast between groups (HCA *minus* CCFS) in the LMR condition showed that activity of the left putamen ($x = -20$, $y = 4$, $z = 10$, z value = 3.54, cluster size = 672 mm^3) and the right putamen ($x = 22$, $y = 4$, $z = 14$, z value = 3.21, cluster size = 616 mm^3) was lower in the CCFS group than in the HCA group. In the HMR condition, there was no difference in bilateral putamen activity between the HCA and CCFS groups.

As presented above, the severity of fatigue (Chalder Fatigue Scale score), LERI reward-from-learning score, and bilateral putamen activities in the LMR condition were different between CCFS and HCA groups. Correlation analyses were performed to clarify the relation between neural activity in reward-sensitivity-related regions and severity of fatigue symptoms or reward value in a learning situation. Activity of the left putamen ($x = -20, y = 4, z = 10$) was negatively and positively correlated with the Chalder Fatigue Scale score (Fig. 3A) and the LERI reward-from-learning score (Fig. 3B), respectively. In addition, there was a trend for the disease duration of CCFS patients to be negatively associated with activity of the left putamen ($r = -0.538$, $P = 0.058$; Fig. 3C) but not the right putamen ($r = -0.449$, $P = 0.123$). Activity of the right putamen ($x = 22$, $y = 4$, $z = 14$) was negatively correlated with the Chalder Fatigue Scale score (Fig. 3D) and there was a trend toward a positive correlation between activity of the right putamen and the LERI reward-from-learning score (Fig. 3E).

Table 2
Performance on monetary reward tasks.

	HCA	CCFS	*P* value
RT in HMR condition (ms)	592 ± 247	681 ± 221	0.344
RT in LMR condition (ms)	588 ± 268	650 ± 208	0.512
RT in NMR condition (ms)	530 ± 223	595 ± 234	0.476

HCA, Healthy children and adolescents; CCFS, childhood chronic fatigue syndrome; RT, Reaction time; HMR, High monetary reward; LMR, Low monetary reward; NMR, No monetary reward. Values are presented as mean ± SD. *P* values were obtained using Student's *t*-test.

4. Discussion

In this study we demonstrated that neural activity of the putamen in CCFS patients was decreased during perception of low-value rewards, but not during perception of high-value rewards, indicating that neural processing in the putamen related to reward sensitivity is impaired in CCFS patients. In addition, putamen activity was correlated with reward from learning in CCFS patients.

The putamen is associated with reward-related learning. Putamen activity has been related to prediction error during reward learning (Schultz et al., 1997). In the context of sequential motor learning, the putamen was more active when a monkey was performing an already-learned motor sequence than when the monkey was learning a new motor sequence (Miyachi et al., 1997, 2002; Hikosaka et al., 1999, 2002). In addition, motivation to learn was correlated with striatal activity, particularly putamen activity (Mizuno et al., 2008). Miike and Bell (2008) reported that low motivation to learn was one of the social disabilities in CCFS patients. Our results suggest that impaired reward processing may decrease reward-related learning and motivation to learn in CCFS patients.

The putamen is part of the brain's reward system. It is innervated by dopaminergic neurons and mediates reward response (Wise, 1985). In adult patients with CFS, 4 weeks of treatment with methylphenidate, a dopamine reuptake inhibitor, reduced the severity of fatigue, suggesting that the dopaminergic function was decreased in these patients (Blockmans et al., 2006). In patients with post-traumatic brain injury, 4 weeks of treatment with methylphenidate also reduced mental fatigue (Johansson et al., 2014). In addition, in children and adolescents with ADHD, 3 months of treatment with osmotic release oral system-methylphenidate improved striatal activity during a low reward condition to the same level as that observed in HCA (Mizuno et al., 2013b), suggesting that decreased dopaminergic activity in the striatum was involved in the decreased reward sensitivity in these patients.

In the present study, activity of the putamen during the low reward condition was associated with the severity of fatigue or disease duration in CCFS patients. As for the alterations of striatal activity, a recent study reported aberrant resting-state functional connectivity of the striatum in adolescents with CFS (Wortinger et al., 2016). Chaudhuri and Behan (2004b) proposed that altered basal ganglia function is a primary

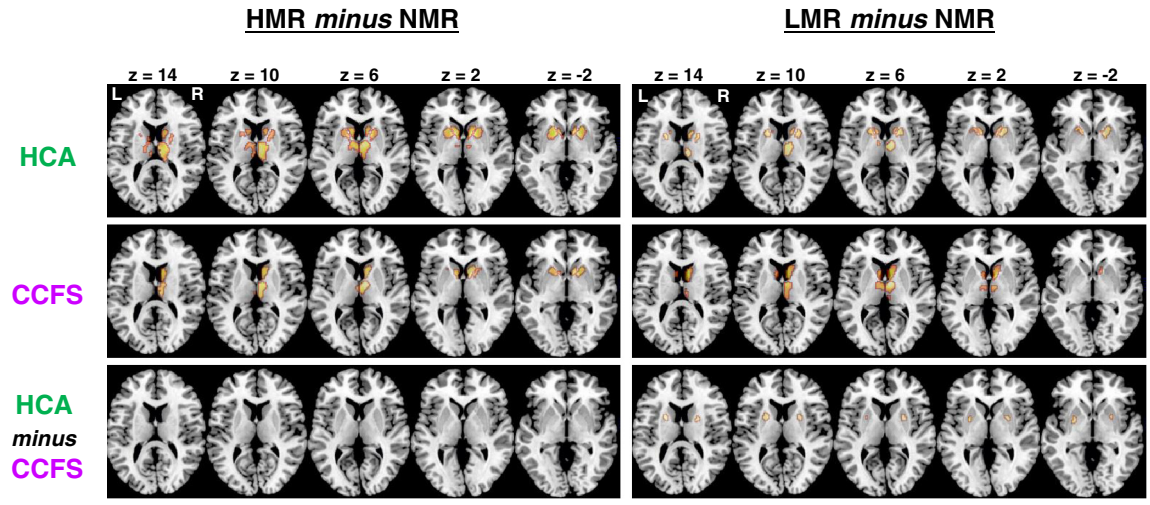

Fig. 2. Activation patterns in the monetary reward task. Statistical parametric maps of HMR (HMR *minus* NMR) and LMR (LMR *minus* NMR) in HCA (top) and CCFS patients (middle) and of the subtraction contrast between study groups (HCA *minus* CCFS) in each reward condition (HMR or LMR *minus* NMR) (bottom). Right (R) and left (L) sides and z-axis (MNI coordinate) are indicated. HMR, high monetary reward; NMR, no monetary reward; LMR, low monetary reward; HCA, healthy children and adolescents; CCFS, childhood chronic fatigue syndrome; MNI, Montreal neurological institute.

mechanism of central fatigue, and that fatigue represents a fundamental behavioral characteristic of diseases that affect the basal ganglia, including Parkinson's disease, multiple sclerosis, cortical stroke, and HIV/AIDS. Treatment studies have reported that dopamine improves fatigue in adult patients with CFS and post-traumatic brain injury patients (Blockmans et al., 2006; Johansson et al., 2014). Fatigue is a symptom of Parkinson's disease, which is a dopaminergic disorder, and treatment with levodopa, a precursor of dopamine, improves fatigue in Parkinson's disease (Feigin et al., 2001). A positron emission tomography imaging study in adult patients with malignant melanoma revealed that glucose metabolism in the putamen (an index of dopamine neurotransmission) was changed by 4 weeks of interferon-alpha treatment, and glucose metabolism in the putamen and nucleus accumbens was associated with severity of fatigue (Capuron et al., 2012). These findings indicate that the severity of fatigue is closely related to dopaminergic function and the activity of dopaminergic neurons in the putamen.

Inflammation in the brain may underlie dopaminergic dysfunction and the decrease in the activity of the putamen during processing of reward sensitivity in CFS (Morris and Maes, 2013). Levels of proinflammatory cytokines in the peripheral blood and cerebral spinal fluid, which might be indicative of neuroinflammation, are higher in adult patients with CFS than in healthy controls (Natelson et al., 2002, 2005), and CCSF patients are less able than healthy controls to transform growth factor-beta1 production, which has an anti-inflammation effect (Tomoda et al., 2005). In addition, we have demonstrated that there is neuroinflammation of widespread brain regions in adult patients with CFS (Nakatomi et al., 2014). In patients with malignant melanoma, treatment with interferon-alpha, which induces production of proinflammatory cytokines, changed dopaminergic activity in the putamen (Capuron et al., 2012). Not only inflammation but also oxidative stress is also associated with dopamine dysfunction in the striatum and substantia nigra (Chung et al., 2010; Villar-Cheda et al., 2010; Juárez Olguín et al., 2016). A recent study suggested that enhancement of oxidative stress in adults with CFS is a potential biomarker for CFS (Fukuda et al., 2016a), and oxidative stress level and symptoms were reduced by 12-weeks supplementation with ubiquinol-10, which has an anti-oxidant effect, in adults with CFS (Fukuda et al., 2016b). Therefore, although further study is needed to confirm the existence of neuroinflammation and oxidative stress and the relation among neuroinflammation, oxidative stress, and neural activity of the putamen in CCFS patients, these findings suggest that inflammation and oxidative stress of the putamen and/or midbrain (where dopaminergic fibres to the putamen originate) may be involved in dopaminergic dysfunction and alterations in reward sensitivity.

Cognitive behavioral therapy for CFS aims to change behavior and cognitions thought to perpetuate symptoms (including the severity of fatigue), and is effective for children and adolescents with CFS (Kawatani et al., 2011) and adults with CFS (Castell et al., 2011; White et al., 2011). Graduated exercise therapy is also effective at reducing the severity of fatigue in adolescents with CFS (Gordon et al., 2010) and adults with CFS (White et al., 2011). In addition, combination treatments with cognitive behavioral therapy and physical training reduced mental fatigue, but did not improve motivation, in patients with cancer-related fatigue (van Weert et al., 2010). These results suggest that, in addition to dopaminergic agents, cognitive behavioral therapy, graduated exercise therapy, or a combination of these may also normalize the neural processing related to altered reward sensitivity and reward-based learning in CCFS patients.

In conclusion, neural processing of reward sensitivity in the putamen was impaired in CCFS patients. For daily tasks with low perceived reward, low putamen activity may induce low motivation to learn. Low putamen activity may be due to dopaminergic dysfunction, and thus, dopamine agents may be an effective treatment for CCFS patients. fMRI enables objective quantification of neural activity in the putamen and can be used to quantify fatigue severity and reward sensitivity. In the future, we aim to conduct a pharmacological fMRI experiment in CCFS patients to evaluate the treatment effect on reward sensitivity.

Financial disclosures

The authors report no biomedical financial interests or potential conflicts of interest.

Author contribution

K.M. took part in the planning and designing of the experiment, data analysis and interpretation and manuscript preparation. J.K., A.T., and T.J. diagnosed and recruited participants with CCFS and performed the experiments. K.T. performed the data analysis and manuscript preparation. A.T.S. conducted the experiments and data analysis and interpretation. T.Y., M.K., and T.H. performed the experiments and data interpretation. Y.W. planned, designed, and supervised the experiments, and participated in data interpretation and manuscript preparation.

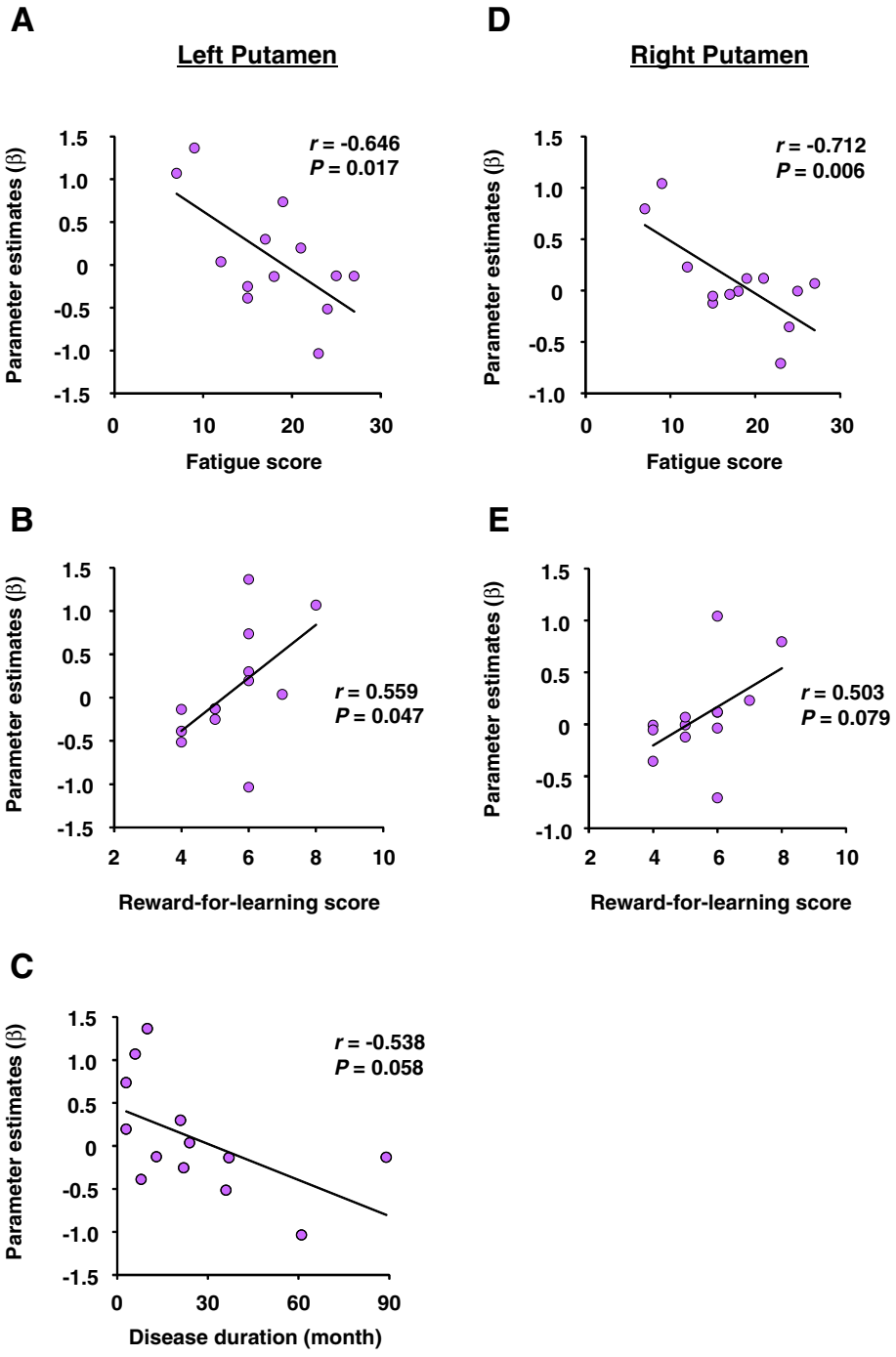

Fig. 3. Correlations between putamen activity and questionnaire scores. Correlations between activity of the left putamen during the low-monetary-reward condition and (A) fatigue score evaluated using the Chalder Fatigue Scale, (B) reward-for-learning score measured as effort-reward imbalance evaluated using the learning model questionnaire, and (C) disease duration, and between activity of the right putamen and (D) fatigue score and (E) reward-for-learning score.

All the authors listed have seen and approved the final manuscript. Furthermore, we have taken due care to ensure the integrity of our work and our scientific reputation.

Acknowledgments

This work was supported by JSPS KAKENHI (25282211 and 16H01874 to K.M.; 24600014 to J.K.; 15K09596 to T.J.; 15H02502 to Y.W.) and partly supported by JST Research Complex Program. We would like to thank Ms. Madoka Kaneko for her excellent technical assistance in participant recruitment. In addition, we would like to thank Mr. Motohira Mio, Ms. Hiroko Ueda, Ms. Niino Iseri, Ms. Eri Uchida, and Ms. Saori Yasuoka for their excellent technical assistance with experiment preparation and Forte Science Communications for editorial help with the manuscript.

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