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

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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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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-