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Impaired neural reward processing in children and adolescents with reactive attachment disorder: A pilot study

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ABSTRACT

Reactive attachment disorder (RAD) is characterized by markedly disturbed and developmentally inappropriate social relatedness due to parental maltreatment. RAD patients often display a high number of comorbid attention deficit/hyperactivity disorder (ADHD) symptoms, and certain RAD symptoms are difficult to discriminate from ADHD. One of the core characteristics of ADHD is a decrease in neural reward processing due to dopamine dysfunction. The aim of the present study was to determine whether the brain activity involved in reward processing in RAD patients is impaired in comparison with ADHD patients and typically developed controls. Five RAD patients, 17 typically developed (TD) controls and 17 ADHD patients aged 10–16 years performed tasks with high and low monetary reward while undergoing functional magnetic resonance imaging. ADHD patients were tested before and after 3 months treatment with osmotic release oral system-methylphenidate. Before treatment, ADHD patients showed that striatal and thalamus activities only in the tasks with low monetary reward were lower than TD controls. RAD patients showed decrease in activity of the caudate, putamen and thalamus during both the high and low monetary reward conditions in comparison with all the other groups. In RAD patients, the activity of the putamen was associated with the severity of posttraumatic stress and overt dissociation. Reward sensitivity was markedly decreased in children and adolescents with RAD, as evidenced by a diminished neural response during reward perception. This suggests that dopaminergic dysfunction exists in these patients, and may inform future dopaminergic treatment strategies for RAD.

1. Introduction

Reactive attachment disorder (RAD) is a Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision (DSM-IV-TR® no. 313.89, American Psychiatric Association, 2000) diagnosis described as markedly disturbed and developmentally inappropriate social relatedness due to parental maltreatment. Children with RAD often display a high number of comorbid attention deficit/hyperactivity disorder (ADHD) symptoms (Minnis et al., 2009). Therefore, certain symptoms of RAD are difficult to discriminate from other disorders, especially those that lie in the domain of ADHD (Follan et al., 2011).

Functional magnetic resonance imaging (fMRI) is useful to identify the neural substrates associated with symptoms of pediatric disease and the neural activity related to the effect of treatments. Our previous fMRI study demonstrated that decreased

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reward sensitivity (i.e., impeded neural responses to smaller rewards), evidenced by decreased activation of the striatum and thalamus during a monetary reward task, and inattention were improved by treatment with dopamine and noradrenaline agents in the form of osmotic release oral system–methylphenidate (OROS–MPH) in pediatric ADHD patients (Mizuno et al., 2013). The aim of the present study was to determine whether brain activity in regions related to reward sensitivity is impaired in pediatric RAD relative to typically developed (TD) subjects and ADHD patients before and after OROS–MPH treatment (btADHD and atADHD, respectively). This is the first fMRI study to observe the brain activity of RAD patients.

2. Methods

The protocol was approved by the Ethics Committees of the University of Fukui, Kumamoto University, and the Aichi Children's Health and Medical Center, and all participants and their parents or directors of the relevant residential foster care facilities gave written informed consent for participation in the study after the study procedures had been explained to them, according to the Declaration of Helsinki. The diagnosis of RAD was confirmed in structured interviews with investigators using the Mini-International Neuropsychiatric Interview for Children and Adolescents after excluding other psychiatric diseases such as mood-related disorders, posttraumatic stress disorder, and substance use disorders, and other neurodevelopmental disorders including ADHD (Sheehan et al., 1998, 2010).

Informed consent was provided by nine patients with RAD (age 10–15 years). Three of the nine patients cancelled their appointment on the day of experiment, and one patient was not able to complete the experiment due to physical deconditioning during the fMRI scans. Using fMRI to study patients with RAD is difficult because these patients are typically afraid of enclosed and dark places and have rapid mood swings. Complete fMRI data were obtained from only five of the nine RAD patients who provided informed consent for the present study. It was very difficult to conduct fMRI experiments in the RAD patients; therefore, the present study provides an invaluable input for identifying the brain-activity dynamics of this patient population. We analyzed the data from the five RAD patients (Table S1). Data from 17 TD subjects and 17 ADHD patients (age 10–16 years) were collected for our previous study (Mizuno et al., 2013). Patients with RAD and ADHD met the DSM-IV-TR criteria (American Psychiatric Association, 2000). ADHD patients were tested before and after receiving OROS–MPH (0.5–1.2 mg/kg per day) for 3 months.

In the MRI scanner, participants performed a simple gambling task (Fig. S1), which was a block-design version of the task used in a previous fMRI study (Izuma et al., 2008; Mizuno et al., 2013). Participants were asked to choose one of three cards by pressing a button. Each card was randomly associated with 0, 30, or 60 yen. The task was performed under three conditions, and each consisted of 8 trials (24 s). 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. Unknown to the participants, the total reward that they could earn in each condition was predetermined. In the high monetary reward (HMR) condition, the participant earned an average of 330 yen (range, 270–390 yen), which was higher than the expected value of the eight trials in the block (240 yen). In the low monetary reward (LMR) condition, the participant earned an average of 150 yen (range, 90–210 yen), which was lower than the expected value. In the no monetary reward (NMR) condition, the outcome presented was always "×××". All participants completed a practice task for 2 min before scanning. During scanning, they performed a total of four sessions. Each session consisted of four blocks of trials from each of the four conditions (HMR, LMR, NMR and fixation rest) and therefore lasted 6 min 24 s (4 blocks × 4 conditions × 24 s per block). 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.

A detailed description of the fMRI acquisition is provided in the Supplemental file. Functional and structural whole-brain images were obtained using echo planar imaging and magnetization-prepared rapid-acquisition gradient-echo sequences, respectively. Data were analyzed using Statistical Parametric Mapping 8 (SPM8). We used a flexible factorial design to compare the activities of reward-level contrasts within the RAD group [(HMR–NMR) and (LMR–NMR)] and between the RAD and other groups by non-repeated measures, as well as compare those between the btADHD and atADHD groups by repeated measures. We defined a priori regions of interest for the caudate, putamen, nucleus accumbens, and thalamus based on the results of our previous study (Mizuno et al., 2013).

3. Results

3.1. Questionnaire results

The clinical characteristics of the five patients with RAD are shown in Table S1. As expected, the Zung Self-rating Depression Scale and Birleson Depression Self-Rating Scale for Children scores were slightly higher than their cut-off points. Scores on the anxiety, depression, anger-hostility, posttraumatic stress, dissociation, and fantasy subscales of the Trauma Symptom Checklist for Children-Alternate (TSCC-A) were lower than the respective cut-off points. Two patients had a child dissociative checklist score and a TSCC-A anger hostility subscale score greater than the cut-off. For the Internal Working Models Scale, all patients had a high score on the ambivalent subscale, one patient had a low score on the secure subscale, and three patients had a high score on the avoidant subscale. Two patients had a history of dissociative disorder and one patient (case 1) had current orthostatic dysregulation. Case 1 was being treated with amezinium-metilsulfate and cases 2 and 4 were being treated with a herbal drug at the time of the fMRI experiment.

3.2. Imaging results

Activity of caudate, putamen, and thalamus was lower in the RAD group in both HMR and LMR conditions (Tables S2–S4). In the HMR + LMR–2NMR contrast, activity of the right caudate and bilateral putamen and thalamus was greater in the TD and atADHD groups than in the RAD group and activity of bilateral caudate, putamen, and thalamus was greater in the btADHD group than in the RAD group ($p < 0.05$, family-wise-error corrected; Fig. 1A). Conjunction analysis among (TD–RAD), (btADHD–RAD) and (atADHD–RAD) contrasts revealed reduced activity of the right caudate and bilateral putamen and thalamus in RAD patients ($p < 0.05$, family-wise-error corrected; Fig. 1B and Fig. S2). Peak values in each region of interest were lowest in RAD patients ($p < 0.01$; Fig. 1C). Severity on the posttraumatic stress and overt dissociation subscale scores of the TSCC-A were negatively correlated with bilateral putamen activity ($p < 0.05$; Fig. 2). There were no other significant correlations between questionnaire scores and activity of the caudate, putamen or thalamus ($p > 0.05$).

4. Discussion

Neural processing for reward sensitivity was severely impaired in RAD patients and was associated with posttraumatic stress and