



## Reduced visual cortex grey matter volume in children and adolescents with reactive attachment disorder



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### ABSTRACT

Child maltreatment increases the risk for psychiatric disorders throughout childhood and into adulthood. One negative outcome of child maltreatment can be a disorder of emotional functioning, reactive attachment disorder (RAD), where the child displays wary, watchful, and emotionally withdrawn behaviours. Despite its clinical importance, little is known about the potential neurobiological consequences of RAD. The aim of this study was to elucidate whether RAD was associated with alterations in grey matter volume (GMV). High-resolution magnetic resonance imaging datasets were obtained for children and adolescents with RAD ( $n = 21$ ; mean age = 12.76 years) and typically developing (TD) control subjects ( $n = 22$ ; mean age = 12.95 years). Using a whole-brain voxel-based morphometry approach, structural images were analysed controlling for age, gender, full scale intelligence quotient, and total brain volume. The GMV was significantly reduced by 20.6% in the left primary visual cortex (Brodmann area 17) of the RAD group compared to the TD group ( $p = .038$ , family-wise error-corrected cluster level). This GMV reduction was related to an internalising problem measure of the Strength and Difficulties Questionnaire. The visual cortex has been viewed as part of the neurocircuit regulating the stress response to emotional visual images. Combined with previous studies of adults with childhood maltreatment, early adverse experience (e.g. sensory deprivation) may affect the development of the primary visual system, reflecting in the size of the visual cortex in children and adolescents with RAD. These visual cortex GMV abnormalities may also be associated with the visual emotion regulation impairments of RAD, leading to an increased risk for later psychopathology.

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### 1. Introduction

Child maltreatment increases the risk for psychiatric disorders throughout childhood and into adulthood [1,2]. Maltreatment encompasses a spectrum of abusive actions (sexual, physical, or emotional abuse) or lack of actions (physical or emotional neglect) by the parent or other caregivers. A psychiatric disorder associated with early life abuse and neglect is reactive attachment disorder (RAD), where the child displays wary, watchful, and emotionally withdrawn behaviours, according to the 5th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5 [3]). Because of emotional dampening, RAD closely resembles internalising disorders with depressive and anxiety

symptoms. In populations of maltreated children in foster care, 19.4–40.0% had signs of RAD based on the DSM-IV criteria [4,5], in which RAD (the inhibited type of RAD) and disinhibited social engagement disorder (DSED; the disinhibited type of RAD) were not completely independent. Even in a general population, the prevalence of RAD based on the DSM-IV criteria has been reported in 1.4% of children and children with RAD are more likely to have multiple comorbidities with other disorders, such as attention deficit hyperactivity disorder (ADHD; 52%), post-traumatic stress disorder (PTSD; 19%), and autism spectrum disorder (ASD; 14%) [6,7]. Despite its high prevalence and clinical importance, there have been very few investigations into the possible neurobiological consequences of RAD.

Of the childhood psychiatric disorders, RAD, which is a negative outcome of child maltreatment, remains one of the least understood phenotype. While most previous studies into RAD have been conducted among Romanian orphans and are limited to children younger than 6 years (for reviews [8,9]), a few studies have recently demonstrated

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that RAD symptoms are reliably identifiable in children older than 6 years [6,10–12]. Historically, RAD (or attachment disorders) was initially defined as a psychiatric disorder in the DSM-III [13] and associated with attachment insecurity as first proposed in Bowlby's attachment theory [14,15]. Now, it is doubted that RAD is closely associated with attachment insecurity in terms of classic attachment theory [10]. Although RAD and DSED were defined as two subtypes (inhibited and disinhibited types) of the same disorder in the DSM-IV criteria, they are now divided into two distinct disorders based on the DSM-5 criteria. According to the DSM-5, children with RAD exhibit wary, watchful, and emotionally withdrawn behaviours, whereas children with DSED display clingy and indiscriminately friendly behaviours even in their interactions with unfamiliar adults. It may also co-occur with ASD, intellectual developmental disorder, or depressive disorders. Although the presence of ASD is considered an exclusionary condition for diagnosing RAD in the DSM-5, the clinical differential diagnosis is complicated by clinical correlates of RAD with 'quasi-autism' [8]. To enhance further our understanding of RAD, it is of particular importance to investigate the nature of the neurobiological mechanisms underlying the behavioural problems of RAD.

Previous neuroimaging studies using structural magnetic resonance imaging (sMRI) techniques have revealed that exposure to early adversity is strongly associated with alterations in brain structure, such as in the grey matter (GM) and white matter (WM) (for reviews [16–19]). According to Teicher and Samson [19], many of the identified neuroanatomical abnormalities are interconnected, and are components of a neurocircuit regulating the stress response to emotional stimuli that includes the thalamus [20], visual or auditory sensory cortex [21–23], medial prefrontal cortex [24–27], hippocampus [28–30], and amygdala [29,31–33]. While the majority of sMRI studies predominantly focus on a priori hypothesised regions and thus provide a constrained characterisation of anatomy, studies into child maltreatment using an unbiased whole-brain analysis approach have been increasingly conducted and have reported similar results as shown in region-of-interest (ROI) studies [16,17]. As for other regions not commonly examined in ROI studies, structural abnormalities in the thalamus and sensory cortex have been revealed for the first time by using such an unbiased whole-brain analysis approach. This approach is helpful to understand the unknown neurobiological abnormalities in RAD associated with child maltreatment.

The aim of this study was to identify structural alterations in regional GM volume (GMV) in maltreated children with RAD using voxel-based morphometry (VBM) as an unbiased whole-brain analysis approach. We sought to assess further whether alterations in regional GMV correlated with psychiatric symptom measures. We hypothesised that RAD, as a negative outcome of child maltreatment, would be associated with alterations in the brain regions that are part of a neurocircuit regulating the stress response to emotional stimuli. Given the general pattern of findings in the related fields [19], we predicted that subjects with RAD, compared to controls without RAD, would be associated with reduced GMV in the thalamus, visual occipital cortex, and prefrontal cortex, and with increased GMV in the auditory temporal cortex. There would not be differences in GMV in the amygdala and hippocampus, especially in the child samples.

## 2. Material and methods

### 2.1. Ethics statement

The study protocol, approved by the Ethics Committees of the University of Fukui, Japan (Assurance no. FU23–43), was conducted in accordance with the Declaration of Helsinki and the Ethical Guidelines for Clinical Studies of the Ministry of Health, Labour and Welfare of Japan. All children and a parent or director of child welfare facilities gave written informed assent and consent for participation in this study. This study is registered with the University Hospital Medical Information Network (UMIN000014655).

### 2.2. Subjects

Twenty-one right-handed medication-naïve 10- to 17-year-old Japanese children (mean age = 12.76 years) with a clinical diagnosis of RAD were recruited from the Department of Child and Adolescent Psychological Medicine at the University of Fukui Hospital from August 2013 to December 2014. The diagnosis of RAD was assessed by licensed child and adolescent psychiatrists (2nd, 6th, and 8th authors) according to the DSM-5 criteria [3]. To exclude other psychiatric conditions (e.g. PTSD, anxiety disorder, and depression), subjects were administered the Mini-International Neuropsychiatric Interview for Children and Adolescents (MINI-KID [34]) and an assessment module of DSM-IV ADHD taken from the Schedule of Affective Disorders and Schizophrenia for School-Age Children, Epidemiologic version (K-SADS-E [35]) by two licensed paediatric-psychological clinicians (2nd and 3rd authors). All of the children had experienced physical, emotional abuse, and/or neglect early in life prior to coming into care. The children were living within a stable placement (in a child welfare facility) even though they were not living with biological parents (for information about child welfare services in Japan [36]). The control subjects, which included 22 typically developing (TD) Japanese children (mean age = 12.95 years) with no history of maltreatment, were recruited from local schools, matched on age, gender, and handedness. All children had normal or corrected vision and normal hearing. There was no difference in the proportion of subjects with corrected vision (for myopia) between the TD (23%) and RAD (24%) groups.

Children were excluded if they had a full scale intelligence quotient (FSIQ) <70 on the Wechsler Intelligence Scale for Children (WISC [37,38]) or the Wechsler Adult Intelligence Scale [39], and left-handedness according to the Edinburgh Handedness Inventory [40]. They were also excluded if they had any history of substance abuse, recent substance use, head trauma with loss of consciousness, significant foetal exposure to alcohol or drugs, perinatal or neonatal complications, neurological disorders, or medical conditions that might adversely affect growth and development.

### 2.3. Psychiatric symptom measures

The Depression Self-Rating Scale for Children (DSRSC; [41]), an 18-item self-report measure, was used to measure depressive symptoms. The Trauma Symptom Checklist for Children (TSCC; [42]), a 54-item self-report measure, was used to evaluate post-traumatic symptoms and other relevant symptoms found in some traumatised children (anger, anxiety, depression, post-trauma stress, dissociation, and sexual concerns). Parents or caregivers in the facilities also completed the Strength and Difficulties Questionnaire (SDQ; [43,44]), a 25-item questionnaire, to assess children's internalising and externalising behaviour problems, as well as prosocial behaviour tendencies. The SDQ internalising behaviour problems are found to be associated with a measure of anxiety symptoms in a sample of children with anxiety disorder [45], which resembles RAD due to emotional regulation impairments. A positive association between the SDQ and Relationship Problems Questionnaire (RPQ) scores has been previously reported [12,46]. The ADHD Rating Scale (ADHD-RS; [47]), an 18-item questionnaire, was used to evaluate inattentive and hyperactive/impulsive symptoms. Symptoms of ADHD have been consistently associated with DSED, but not RAD [8,48]. The Autism Spectrum Quotient (AQ [49]), a 50-item questionnaire, was completed by a parent or caregiver to evaluate ASD traits, such as social skills, attention switching, attention to detail, communication, and imagination. The presence of ASD is an exclusionary condition for the diagnosis of RAD [3].

### 2.4. MRI acquisition

All subjects were scanned on a 3-Tesla MR scanner (Discovery MR 750; General Electric Medical Systems, Milwaukee, WI, USA)

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