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Type and timing of childhood maltreatment and reduced visual cortex volume in children and adolescents with reactive attachment disorder

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A R T I C L E I N F O

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A B S T R A C T

Reactive attachment disorder (RAD) is a severe social functioning disorder associated with early childhood maltreatment where the child displays emotionally withdrawn/inhibited behaviors toward caregivers. Brain regions develop at different rates and regions undergoing rapid change may be particularly vulnerable during these times to stressors or adverse experiences. The aim of this study was to investigate the effect of type and timing of childhood adversities on structural alterations in regional gray matter (GM) volume in maltreated children with RAD.

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). Structural images were analyzed using a whole-brain voxel-based morphometry approach and the type and timing of maltreatment, which may be more strongly associated with structural alterations, was assessed using random forest regression with conditional inference trees.

Our findings revealed that there is a potential sensitive period between 5 and 7 years of age for GM volume reduction of the left primary visual cortex (BA17) due to maltreatment. We also found that the number of types of maltreatment had the most significant effect on GM volume reduction and that the second most significant variable was exposure to neglect.

The present study provides the first evidence showing that type and timing of maltreatment have an important role in inducing structural abnormalities in children and adolescents with RAD.

1. Introduction

Reactive attachment disorder (RAD) is a severe social functioning disorder associated with early childhood maltreatment where the child displays emotionally withdrawn/inhibited behaviors toward caregivers according to the 5th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) (American Psychiatric Association, 2013). The prevalence of RAD based on the DSM-IV criteria, in which RAD (the inhibited type of RAD) and disinhibited social engagement disorder (the disinhibited type of RAD) are not completely independent, is reportedly 19.4–40.0% among maltreated children in foster care (Lehmann et al., 2013; Zeanah et al., 2004) and 1.4–2.4% among children in the general population (Minnis et al., 2013). Children with RAD are more likely to have multiple comorbidities, such as with attention deficit-hyperactivity disorder (52%), post-traumatic stress disorder (PTSD; 19%), and autism spectrum disorder (14%) (Minnis et al., 2013; Pritchett et al., 2013). Thus, although RAD has high prevalence and presents with various difficulties on pathological assessment, there have been very few investigations into the possible neurobiological consequences of RAD.

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The childhood brain is considered to have specific temporal sensitivity for each brain region in terms of both structure and function (Andersen and Teicher, 2008; Andersen et al., 2008). Adverse experiences during these sensitive periods may affect brain organization, which is under rapid development, such as synaptic production, pruning, and myelination (Teicher et al., 2002). From the perspective of neurobiology, the brain during childhood is highly plastic and develops by constant modification based on gene-environment interactions (Teicher and Samson, 2013). The developmental curves of cortical gray matter volume are regionally specific and have distinctive trajectories for each local region (Giedd et al., 1999; Gogtay et al., 2004). Therefore, the reactivity of the brain to the developmental environment may also differ depending on the developmental stage. Similarly, a number of previous studies has shown that different types of adversity exert effects on different brain areas (Choi et al., 2009; Choi et al., 2012; Heim et al., 2013; Tomoda et al., 2011; Tomoda et al., 2012). Thus, it also seems that the clinical phenotypes of maltreatment during childhood may partially depend on the type or timing of exposure to adversities (Khan et al., 2015; Schalinski and Teicher, 2015; Teicher et al., 2018).

The aim of this study was to investigate the effect of type and timing of childhood adversities on structural alterations in regional gray matter (GM) volume in maltreated children with RAD. In our previous study, we found that children and adolescents with RAD exhibit structural abnormalities in the left primary visual cortex (BA17) (Shimada et al., 2015). Similar to the trends found in related studies (Andersen and Teicher, 2008; Andersen et al., 2008; Tomoda et al., 2011; 2012), we hypothesized that structural abnormalities in RAD would be dependent on the type or timing of the maltreatment. Hence, we sought to determine if there were windows of vulnerability across age and type of maltreatment for structural alteration in children and adolescents with RAD.

2. Methods

Subject information, such as demographic and clinical characteristics of RAD and typically developing (TD) groups, the acquisition condition, and processing of the structural imaging data have been described in our previous study (Shimada et al., 2015) where further details can be found.

2.1. Participants

Twenty-one medication-naive 10- to 17-year-old children with a clinical diagnosis of RAD participated in the study (mean age = 12.8 years; 13 girls), as previously reported (Shimada et al., 2015). Participants were right handed and their race/ethnicity was Japanese. Participants were recruited from the Department of Child and Adolescent Psychological Medicine at the University of Fukui Hospital. RAD was assessed through structured interviews by three licensed pediatric-psychiatric clinicians according to the DSM-5 criteria (American Psychiatric Association, 2013). Information about type and timing of exposure to maltreatment was collected by child welfare facility staffs who knew the background of a participating child well. The number of children who had experienced physical abuse, emotional abuse, sexual abuse, and neglect was seven (33.3%), 11 (52.4%), two (9.5%), and 16 (76.2%), respectively, when multiple responses for maltreatment types were allowed. The mean duration of exposure was 7.7 ± 4.68 years. The Mini-International Neuropsychiatric Interview for Children and Adolescents was administered to exclude other psychiatric conditions (e.g., PTSD) (Sheehan et al., 2010). All children had experienced physical and/or emotional abuse and/or neglect early in life prior to coming into care. The Trauma Symptom Checklist for Children (TSCC) (Briere, 1996), a 54-item self-report measure, was used to evaluate post-traumatic and other relevant symptoms found in some traumatized children (anger, anxiety, depression, post-traumatic stress, dissociation, and sexual concerns). Twenty-two TD children with no history of maltreatment were recruited as control participants from local schools or communities via advertisements, matched for age, sex, handedness, and race/ethnicity (mean age = 12.95 years; 12 girls). It was also confirmed that the TD children had no disorders meeting the DSM-IV criteria for any major Axis I and Axis II disorders (American Psychiatric Association, 1994). Participants who had a full-scale intelligence quotient (FSIQ) < 70 on the Wechsler Intelligence Scale for Children-Fourth Edition (WISC-IV) or the Wechsler Adult Intelligence Scale-Third Edition (WAIS-III) (Wechsler, 1997; Wechsler, 2003) were excluded. The study protocol was approved by the Ethics Committees of the University of Fukui and was conducted in accordance with the Declaration of Helsinki. All children and a parent or director of child welfare facilities provided written informed assent and consent for participation in this study.

2.2. Brain imaging and analysis

Image acquisition was performed using a 3-Tesla scanner (Discovery MR 750; General Electric Medical Systems, Milwaukee, WI) with a 32-channnel head coil. A T1-weighted anatomical dataset was obtained from each subject by fast spoiled gradient recalled imaging sequence (voxel size $1 \times 1 \times 1$ mm, echo time = 1.996 ms, repetition time = 6.38 ms, inversion time = 600 ms, flip angle = 11°, total scan time = 4 min 50 s).

Voxel-based morphometry was performed using Statistical Parametric Mapping version 12 (SPM12) (Wellcome Department of Imaging Neuroscience, University College London, London, UK; http://www.fil.ion.ucl.ac.uk/spm/software/spm12/) implemented in MATLAB 9.5 (Math-Works Inc., Natick, MA). The T1-weighted images were coarsely segmented into GM, white matter (WM), cerebrospinal fluid, and skull/scalp compartments using tissue probability maps. The Diffeomorphic Anatomical Registration through Exponentiated Lie Algebra (DARTEL) algorithm was applied to the segmented brain tissues to generate a study-specific template and to achieve an accurate inter-subject registration with improved realignment of smaller inner structures. The segmented GM images were spatially normalized into the Montréal Neurological Institute (MNI) space and were written out with an isotropic voxel resolution of 1.5 mm. Any volume change induced by normalization was adjusted via a modulation algorithm. Spatially normalized GM images were smoothed by a Gaussian kernel of 8 mm full width at half maximum.

Regional differences in GM volume between groups were analyzed in SPM 12 using two-sample *t*-test models. Potential confounding effects of age, sex, Full Scale Intelligence Quotient, and total brain volume (calculated as the sum of GM and WM volumes) were modeled and variances attributable to them were excluded from the analyses. A whole-brain analysis with correction for multiple comparisons at the cluster level was conducted to examine regional differences in GM volume between the groups. The statistical threshold was set at $p < 0.001$ at the voxel level and $p < 0.05$ with family-wise error correction for multiple comparisons at the cluster level. The anatomical localization of significant clusters was investigated with the Automated Anatomical Labeling and Brodmann area (BA) atlases implemented in the MRIcron software package (Rorden et al., 2007).

2.3. Random forest regression with conditional trees

The presence of a potential ‘sensitive period,’ during which exposure to childhood maltreatment may be more strongly associated with regional alterations in GM volume, was assessed using random forest regression with conditional inference trees (‘cforest’in R package party; (Strobl et al., 2007)), as we have used in previous studies (Pechtel et al., 2014; Schalinski and Teicher, 2015; Teicher et al., 2018; Tomoda et al., 2012). This is a form of machine learning in which a large number of unpruned decision trees are generated and their results