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Effects of cross-rearing with social peers on myelination in the medial prefrontal cortex of a mouse model with autism spectrum disorder

Manabu Makinodan^{a,*}, Kazuki Okumura^a, Daisuke Ikawa^a, Yasunori Yamashita^a, Kazuhiko Yamamuro^a, Michihiro Toritsuka^a, Sohei Kimoto^a, Takahira Yamauchi^a, Takashi Komori^a, Yoshinori Kayashima^a, Hiroki Yoshino^a, Akio Wanaka^b, Toshifumi Kishimoto^a

^a Department of Psychiatry, Nara Medical University School of Medicine, 840 Shijo-cho, Kashihara, Nara 634-8522, Japan

^b Department of Anatomy and Neuroscience, Nara Medical University School of Medicine, 840 Shijo-cho, Kashihara, Nara 634-8522, Japan

* Corresponding author.

E-mail address: mmm@naramed-u.ac.jp (M. Makinodan).

Abstract

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by impaired social interaction, poor communication skills, and repetitive/restrictive behaviors. Recent studies have indicated that early rehabilitative intervention can alleviate the symptoms of individuals with ASD. However, it remains unknown whether rehabilitative intervention can restore brain structures such as myelin, which generally shows abnormalities in individuals with ASD. Therefore, in the present study, we used a mouse model of ASD (BTBR mice) that demonstrated asocial behaviors and hypomyelination in the medial prefrontal cortex (mPFC) to investigate whether interaction with social peers (C57BL/6J mice) has an effect on myelination. We found that housing with C57BL/6J mice after weaning through adulthood increased the myelin thickness in mPFC, but not in the motor cortex, of BTBR mice. There was no effect of cross-rearing with C57BL/6J mice on axon

diameter in mPFC of BTBR mice. This finding suggests that early rehabilitative intervention may alleviate myelin abnormalities in mPFC as well as clinical symptoms in individuals with ASD.

Keywords: Neuroscience, Psychology, Psychiatry

1. Introduction

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by two core symptoms, namely impaired social interaction and communication, and repetitive behaviors. Despite a number of studies conducted to elucidate the remedy, there are few established treatments for symptom improvement. However, recent studies have indicated the effectiveness of rehabilitative interventions to alleviate the social problems of individuals with ASD, and substantial efforts have been devoted to the development of such rehabilitative interventions. The most common rehabilitative intervention is applied behavioral analysis (ABA), which is an intense behavioral intervention that improves intellectual and educational functioning (Lovaas, 1987). Several brain imaging studies using functional magnetic resonance imaging (fMRI) revealed that rehabilitative interventions, including computer-based facial affect recognition training, pivotal response treatment, and reading intervention, can improve ASD symptoms by affecting brain functions and connectivity (Calderoni et al., 2016). However, to the best of our knowledge, no studies have confirmed the effects of rehabilitative interventions on brain structures such as myelin, which is reportedly altered in individuals with ASD (Zikopoulos and Barbas, 2010).

Numerous mouse models of ASD have been developed and investigated to extrapolate the pathobiology of ASD. Among these, the BTBR mouse is a widely used model of ASD with substantial face validity that demonstrates impaired social interaction, aberrant ultrasonic vocalization as communication problems, increased grooming as a repetitive behavior, and abnormalities of immune cells and oligodendrocyte lineage cells (Yang et al., 2007, 2011; Heo et al., 2011; Stephenson et al., 2011). In order to examine the effects of rehabilitative intervention, BTBR mice were cross-fostered and cross-reared with C57BL/6J mice, which have high sociability and low repetitive behaviors. Interestingly, cross-fostering with C57BL/6J mice from birth through weaning did not alter the behaviors of BTBR mice (Yang et al., 2007); however, cross-rearing with C57BL/6J for 20 or 40 days after weaning significantly resolved sociability deficits (Yang et al., 2011). These findings indicated that social intervention after weaning can change ASD-like behaviors and, most probably, other associated brain functions.

Myelin is a laminated membrane structure surrounding axons produced by oligodendrocytes, and it accelerates the axonal conduction velocity (McKenzie et al., 2014). Multiple studies have revealed that oligodendrocytes and myelin are

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