Minireviews

Involvement of Neuroinflammation during Brain Development in Social Cognitive Deficits in Autism Spectrum Disorder and Schizophrenia

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ABSTRACT

Development of social cognition, a unique and high-order function, depends on brain maturation from childhood to adulthood in humans. Autism spectrum disorder (ASD) and schizophrenia have similar social cognitive deficits, although age of onset in each disorder is different. Pathogenesis of these disorders is complex and contains several features, including genetic risk factors, environmental risk factors, and sites of abnormalities in the brain. Although several hypotheses have been postulated, they seem to be insufficient to explain how brain alterations associated with symptoms in these disorders develop at distinct developmental stages. Development of ASD appears to be related to cerebellar dysfunction and subsequent thalamic hyperactivation in early childhood. By contrast, schizophrenia seems to be triggered by thalamic hyperactivation in late adolescence, whereas hippocampal aberration has been possibly initiated in childhood. One of the possible culprits is metal homeostasis disturbances that can induce dysfunction of blood-cerebrospinal fluid barrier. Thalamic hyperactivation is thought to be induced by microglia-mediated neuroinflammation and abnormalities of intracerebral environment. Consequently, it is likely that the thalamic hyperactivation triggers dysregulation of the dorsolateral prefrontal cortex for lower brain regions related to social cognition. In this review, we summarize the brain aberration in ASD and schizophrenia and provide a possible mechanism underlying social cognitive deficits in these disorders based on their distinct ages of onset.

Introduction

Microglial cells contribute to immune surveillance in the central nervous systems (CNS), and polarization of microglial subsets (M1 and M2) plays an important role in controlling the balance between promotion and suppression in neuroinflammation (Ransohoff and Perry, 2009; Kettenmann et al., 2011; Mikita et al., 2011; Saijo and Glass, 2011). M1 microglial cells can promote neuroinflammation and subsequent neural network dysfunction in the CNS, whereas M2 microglia are implicated in inhibiting inflammation and restoring homeostasis (Mosser and Edwards, 2008; Gordon and Martinez, 2010). As we reported previously, imbalance of M1 and M2 microglia appears to be closely related to mood aberration of major depressive disorder and bipolar disorder (Nakagawa and Chiba, 2014, 2015). Autism spectrum disorder (ASD) is defined by deficits in social communication interaction and behavioral flexibility, manifesting in early childhood (Volkmar et al., 2014). Eighteen surveys conducted according to the Diagnostic and Statistical Manual of Mental Disorders, fourth edition, criteria demonstrated that estimates of the rate of ASD range from 10 in 10,000 to 16 in 10,000, whereas the most recent study estimated the prevalence in the United States as 11.3 in 1,000, suggesting that the prevalence of ASD is increasing (Volkmar et al., 2014). Parents of children with ASD have often reported that the first sign of a problem with their child was the delay of language in the second year of life (Tager-Flusberg, 2000). Social cognitive deficits are a hallmark characteristic of ASD and schizophrenia (Couture et al., 2006; Meyer et al., 2011a).

Schizophrenia is characterized by positive, negative, and cognitive symptoms and afflicts approximately 1% worldwide; it develops in late adolescence most frequently (Stahl, 2013). It
is postulated that dopamine hyperactivity in the nucleus accumbens induced by hypofunction of glutamate receptors in the prefrontal cortex and hippocampus is related to positive symptoms, whereas hypoaivation of dopamine and glutamate neurons in the prefrontal cortex contributes to negative symptoms (Stahl, 2013). In contrast, according to the neurodevelopmental hypothesis, the etiology of schizophrenia appears to involve pathologic processes that are caused by genetic and environmental risk factors and begin before the brain fully matures (Weinberger, 1986; Mareno and Weinberger, 2000).

Pathogenesis of these disorders is complex and contains several features, including genetic risk factors, environmental risk factors, and sites of abnormalities in the brain (Hultman et al., 1999; Gardener et al., 2011; Miles, 2011; Onore et al., 2012). Recently, Meyer et al. (2011a), focusing on similarities and differences between schizophrenia and ASD, implied that disturbed neurodevelopment by maternal infection and succeeding prenatal neuroinflammation is shared by ASD and schizophrenia, whereas persistent and latent neuroinflammation contributes to onset of ASD and schizophrenia, respectively. However, these hypotheses seem not to clarify how brain alterations associated with symptoms in these disorders develop at distinct developmental stages. Therefore, in this article, we summarize the brain aberration and related neuroinflammation in early and chronic phases of ASD, discuss similarities and differences between social cognitive deficits in ASD and those in schizophrenia, and provide a possible mechanism underlying the social cognitive deficits in these disorders.

**ASD and Neuroinflammation**

**Genetic Risk Factors.** Although there has been considerable debate in etiology of ASD, the genetic basis of this disorder is supported by several twin studies (Rosenberg et al., 2009; Frazier et al., 2014). Much attention has been focused on a relationship between ASD and a transcriptional gene, forkhead box P2 (FOXP2), which is closely related to language ability (Bowers and Konopka, 2012). FOXP2 protein regulates gene expression of MET (Mukamel et al., 2011) and contactin-associated protein-like 2 (CNTNAP2) (Arking et al., 2008; Bowers and Konopka, 2012). During gestation, MET gene is selectively expressed in the temporal and occipital lobes, which contribute to verbal communication, implying that MET plays an important role in development of language ability (Mukamel et al., 2011). The CNTNAP2 encodes a cell adhesion molecule of neurexin subfamily and is highly expressed in frontal lobe circuits in the developing human brain (Arking et al., 2008). It has been reported that common variants in CNTNAP2 are associated with several allied neurodevelopmental disorders, including ASD (Scott-Van Zeeland et al., 2010). FOXP2 mutant mice show ASD-like phenotypes, such as reduced or atypical vocalizations and impairments of learning performances (Shu et al., 2005; Fujita et al., 2008; Kurt et al., 2012).

Other studies demonstrated that ASD symptoms are associated with gene variations of neuroligin, neurexin, Src homology and multiple ankyrin repeat domain 3, and cell adhesion molecule 1 (Ziling et al., 2008; Bourgeron, 2009; Fujita-Jimbo et al., 2015). The variations of these synaptic cell adhesion molecules seem to induce an imbalance of excitatory and inhibitory receptors and synaptic pruning deficits (Lisé and El-Husseini, 2006; LeBlanc and Fagioli, 2011). In the process of synaptic pruning, upregulation of myocyte enhancer factor 2 can lead to ubiquitination of postsynaptic density protein 95 (PSD-95) in the postsynaptic density, and, subsequently, the degradation of ubiquitinated PSD-95 results in a synapse elimination (Caroni et al., 2014). Interestingly, mutated neurelin 3 or cell adhesion molecule 1 protein upregulates C/EBP-homologous protein, a marker of endoplasmic reticulum stress, suggesting that the synaptic pruning deficits induce endoplasmic reticulum stress and neuroinflammation in ASD (Fujita et al., 2010; Fujita-Jimbo et al., 2012, 2015). Consequently, these genetic factors presumably influence function of neural circuitry of social cognition in combination with environmental risk factors.

**Environmental Risk Factors.** Air pollutants, pesticides, polychlorinated biphenyls, solvents, and glyphosate appear to be associated with development of ASD (Sealey et al., 2016). A possible relationship is shown between ASD severity and blood or hair levels of heavy metals, including mercury and lead (Rossignol et al., 2014). A recent study revealed that some of ASD may be caused by maternal antibodies to fetal brain antigens such as cypin, which, along with PSD-95, can regulate dendritic branching of hippocampal neurons (Braunschweig et al., 2013). Sodium valproate, an anticonvulsant and a mood stabilizer, induces fetal neurodevelopment aberration in animals, including humans, higher incidence of ASD in humans, and ASD-like phenotypes such as reduced social interaction and increased repetitive behaviors in rodents (Roulet et al., 2013). There are many prenatal and postnatal risk factors, as follows: maternal medication use, C-reactive protein levels, hypertension, hemorrhage, infection, depressive symptomatology, food, gestational diabetes, parental age at birth, prolonged labor, fetal distress, birth injury or trauma, multiple birth, low birth weight, etc. (Glasson et al., 2004; Gardener et al., 2009, 2011; Lupien et al., 2011; Patterson, 2011; Guinchat et al., 2012; Neggies, 2014; Xiang et al., 2015).

**Metal Homeostasis Disturbances.** It is highly probable that a well-balanced diet plays an essential role in development and maintenance of brain functions, because good nutrition is a cornerstone of good health, whereas poor nutrition is associated with reduced immunity, impaired physical development, and reduced productivity (World Health Organization, 2016). Children with ASD often have restricted diets that can lead to nutrient deficiencies with brain metal homeostasis disturbances (Bilic et al., 2010; Sidrak et al., 2014). Iron deficiency is one of the most prevalent types of malnutrition, affecting probable two billion people in the world, and pregnant women and young children are affected most severely, because pregnancy and infant growth demand iron (World Health Organization, 2016). Iron is required for basic cellular functions in all of the tissues, especially in the brain and muscle, and is critically important for the oxygen-carrier function of hemoglobin in red blood cells (Breymann, 2015). In the brain, iron is transported by transferrin or divalent metal transporter-1 from the peripheral blood and is essential for the activity of several enzymes involved in myelination process and monoamine neurotransmitter synthesis (Dusek et al., 2015). Iron deficiency is suggested to be related to development of ASD (Bilic et al., 2010; Sidrak et al., 2014). Lower iron concentrations in the blood appear to induce transport of neurotoxic manganese.
instead of iron into the brain (Gunter et al., 2013; Dusek et al., 2015).

When zinc levels are decreased and conversely copper levels are increased in the blood during pregnancy, prevention of fetal development would be introduced (Faber et al., 2009). The imbalance of zinc and copper levels may deteriorate FOXP2 functions and induce language disability, because FOXP2 contains zinc finger domain (Bowers and Konopka, 2012). Indeed, it has been reported that ASD children show reduced zinc levels in their hairs and low blood zinc/copper ratio (Faber et al., 2009; Yasuda et al., 2011, 2013). Taken together, it is possible that metal homeostasis disturbances are one of the primary culprits of ASD.

**Involvement of Neuroinflammation.** A ligand for the peripheral benzodiazepine receptor, \([11C]-(R)-(1-[2-chlorophenyl]-N-methyl-N-[1-methylpropyl]-3-isooquinoline carboxamide) ([11C]PK11195), can be used for the imaging of activated microglia cells with positron emission tomography (Banati, 2002). It has been reported that [11C]PK11195–binding potential values are significantly higher in the brain regions, including the cerebellum, midbrain, fusiform gyrus, and prefrontal cortex in ASD adults as compared with controls (Suzuki et al., 2013). In the visual cortex in autopsy brains, microglial densities are significantly greater in individuals with ASD versus controls (Tetreault et al., 2012). An immunohistochemical study revealed that a marked activation of microglia and astrocytes in the middle frontal and anterior cingulate gyrus and cerebellum is obtained at autopsy from ASD subjects (Vargas et al., 2005). Similarly, microglial cells are markedly activated in the dorsolateral prefrontal cortex (DLPFC) of ASD individuals (Morgan et al., 2010). Risperidone in combination with a cyclooxygenase-2 inhibitor, celecoxib, showed a superior efficacy as compared with monotherapy of risperidone in a randomized double-blind placebo-controlled clinical study in ASD children (Asadabadi et al., 2013). From these results, neuroinflammation mediated by M1 microglia appears to be associated with ASD.

Postmortem studies revealed prominent microglia activation and increased proinflammatory cytokines and chemokines, including interferon-γ (IFN-γ), interleukin (IL)-1β, IL-6, IL-12p40, tumor necrosis factor-α, and CC-chemokine ligand 2 (CCL2) in the brain, particularly in the frontal cortex, cerebellum, and cerebrospinal fluid (CSF) of ASD individuals (Vargas et al., 2005; Li et al., 2009; Morgan et al., 2010; Onore et al., 2012). Similarly, the levels of IL-1β, IL-6, IL-8, IL-12p40, CCL2, CCL5, and CCL11 are significantly increased in the plasma of ASD individuals (Ashwood et al., 2011a, b). The increased cytokine levels were predominantly in children who had a regressive form of ASD and were associated with more impaired communication and aberrant behaviors (Ashwood et al., 2011a, b). Furthermore, BTBR Tita/J mice with gene mutation in kynurenine 3-hydroxylase (Kmo) related to neuroprotective actions show elevated levels of proinflammatory cytokines, including IL-1β and IL-6 in the cerebellum and ASD-like phenotypes such as reduced social interactions and impaired juvenile play (McFarlane et al., 2008; Heo et al., 2011). In contrast, the levels of IL-4 and IL-10 in the plasma showed no difference between ASD and control subjects (Ashwood et al., 2011b). The levels of transforming growth factor-β in ASD blood are significantly lower as compared with typically developing controls and are negatively correlated with psychologic symptom severity (Okada et al., 2007; Ashwood et al., 2008).

Therefore, it is highly possible that neuroinflammation mediated by M1 microglia is associated with symptoms of ASD based on imbalance of proinflammatory M1 and anti-inflammatory M2 polarization states of microglia. Our view is along the lines of previous hypotheses that the imbalance of M1/M2 polarization of microglia is implicated in neuroinflammation and disruption of excitatory versus inhibitory balance in the brain of ASD (Gottfried et al., 2015; Koyama and Ikegaya, 2015).

**Disturbances in the Blood-Brain Barrier.** The blood-brain barrier (BBB) has a unique barrier structure between the lumen of cerebral blood vessels and brain parenchyma. The endothelial cells have luminal tight junction and are surrounded by basement membrane and the pericytes. Around all of these structures are the astrocytic end feet processes from nearby astrocytes. The interaction among vascular endothelial cells, pericytes, and astrocytes plays an important role in maintenance of BBB functions (Abbott et al., 2006; Bonkowski et al., 2011). It is possible that BBB dysfunction contributes to major depressive disorder and schizophrenia (Shalev et al., 2009).

Maternal hyperglycemia and hypertension are often associated with activation of inflammatory cells, inducing abnormalities in capillary endothelial cells of the brain (Jackson, 2011). In the inflamed capillaries, proinflammatory cytokines and mediators contribute to the polarization and recruitment of M1 macrophages (Jackson, 2011). At early phase, M1 macrophages appear to remove injured vascular endothelial cells by phagocytosis (Jackson, 2011; Phillipson and Kubes, 2011); however, under insufficient M2 condition, M1 macrophages can probably induce prolonged inflammation and destruction of BBB. The BBB possesses manganese sensitivity (Bornhorst et al., 2012), suggesting that disequilibrium of iron and manganese levels is presumably associated with dysfunction of BBB directly. Imbalance of zinc and copper levels may contribute to dysfunction of astrocytes because astrocytes express copper, zinc (CuZn) superoxide dismutase-1 (SOD-1) activity (Chen et al., 2006). Taken together, it is likely that dysfunction of BBB is caused by multiple prenatal and postnatal risk factors. Because BBB function is immature at early developmental stages (Saunders et al., 2014), cerebral neural cells in fetuses, infants, and young children are presumably vulnerable to these factors. Therefore, it is possible that BBB disturbances are related to ASD.

**Disturbances in the Blood-CSF Barrier.** The blood-CSF barrier (BCB) lies between the choroid plexus vessels in circumventricular organs (CVOs) and the CSF (Choi and Kim, 2008; Benarroch, 2011; Lun et al., 2015). The CVOs are found to be located around the cerebral ventricles, and the CVOs with BCB are characterized by lack of BBB properties (Choi and Kim, 2008; Benarroch, 2011). In the BCB, tanyocytes, highly specialized ependymal cells, have tight junction and play regulatory roles in interaction among the blood, brain parenchyma, and CSF (Benarroch, 2011; Langlet et al., 2013). Tanyocytes contribute to monitoring the CSF composition (Sisó et al., 2010; Benarroch, 2011), and these cells seem to be vulnerable to imbalance of zinc and copper levels because tanyocytes express CuZn SOD-1 (Peluffo et al., 2005). Furthermore, the BCB is thought to be a major route for manganese into the CSF because the increased blood manganese levels can induce more severe dysfunction of the BCB rather than BBB (Bornhorst et al., 2012). Therefore, it is highly probable...
that maternal disturbances of cellular metal homeostasis predominantly induce dysfunction of tanycytes in the BCB and subsequent neuroinflammation that triggers aberration of neural network in fetuses, infants, and young children (Fig. 1).

Social Cognitive Deficits in ASD

Cognitive function such as self-regulation and social cognition enables humans to make plans and regulate actions in social situations appropriately (Heatherton and Wagner, 2011). This unique cognitive function depends on brain maturation from childhood to adulthood in humans (Lebel et al., 2008; Catts et al., 2013). Therefore, it is likely that immaturity negatively impacts high-order cognition acquired at each developmental stage.

**Dysfunction of the Cerebellum.** Young children with ASD (2–4 years of age) show a significant increase in cerebellar volume as compared with typically developing children, whereas cerebellar volume of ASD schoolchildren and adolescents is similar to or rather smaller than controls (Sparks et al., 2002; Allen, 2005; Anagnostou and Taylor, 2011). A diffusion tensor imaging study to investigate brain anatomic connectivity indicated a significant increase in fractional anisotropy, the deviation from pure isotropic diffusion of water mobility, in the brain regions including cerebellum of young children with ASD (1–6 years of age) (Weinstein et al., 2011). In contrast, fractional anisotropy in the cerebellum is decreased in ASD schoolchildren (6–12 years old) (Brito et al., 2009). Serotonin transporter binding is reduced in several brain regions, including cerebellum of ASD adults (Nakamura et al., 2010). Furthermore, [11C](R)-PK11195–binding values are significantly higher in the brain regions including cerebellum of ASD adults as compared with those of controls (Suzuki et al., 2013). From these results, it is possible that neuronal hyperactivation and neuroinflammation occur in the cerebellum of young children with ASD, subsequently leading to reduction of neuronal activity and atrophy with persistent neuroinflammation in the cerebellum of ASD schoolchildren, adolescents, and adults.

The cerebellum is involved in body and limb movement, executive and cognitive functions, and language ability (Koziol et al., 2014; Wang et al., 2014). ASD individuals often show motor abnormalities consistent with cerebellar dysfunction that occurs in young children and is persistent over time (Lee and Bo, 2015). Although cerebellar lesions are unlikely to result in profound cognitive deficits in adults, cerebellar abnormalities at earlier ages lead to more conspicuous cognitive and affective changes, diagnosed as cerebellar cognitive-affective syndrome (Wang et al., 2014). Cerebellar cognitive-affective syndrome is characterized by disturbances of executive function, impaired spatial cognition, personality change, and linguistic difficulties (Schmahmann and Sherman, 1998). It has been hypothesized that the cerebellum plays a pivotal role in cognition in young children within the critical period (2–4 years of age) and contributes to body and limb movement at every developmental stage (Wang et al., 2014). Thus, one could speculate that cerebellar aberration in young children is associated with initiation of social cognitive deficits in ASD.

As mentioned in the above section, impaired cellular metal homeostasis can induce disturbances of cerebral ventricles and contributes to functional or structural alterations in the brain. Because the cerebellum is located adjacent to the fourth ventricle and the cerebral ventricles are partly surrounded by the choroid plexus in young children (Su and Young, 2011; Liddelow, 2015), impaired cellular metal homeostasis probably induces hyperactivation of the cerebellum via dysfunction of choroid plexus and fourth ventricle in young children with ASD. Neuronal hyperactivation can trigger M1 polarization of microglia in the cerebellum, and then M1 microglial-mediated neuroinflammation and neural network dysfunction may extend to the related tissues under inhibition in the M2 state. Consequently, it is possible that imbalance between M1 and M2 polarization of microglia plays an important role in the progression of ASD (Nakagawa and Chiba, 2014, 2015).

It is unlikely that symptoms of ASD can be caused by abnormalities in a single brain region because a significant reduction in total gray matter volume and a marked increase in cerebral ventricular volume are observed in ASD schoolchildren, adolescents and adults (McAlonan et al., 2005). There are neuronal connections between the cerebellum and other brain regions (Mazzola et al., 2013; Rogers et al., 2013; Koziol et al., 2014). To understand symptoms, initiation, and progression of ASD more precisely, it is important to analyze the neuropathological relation between the cerebellum and other brain regions.

![Fig. 1. The cerebral ventricles, BBB, and BCB.](https://example.com/figure1.png)
Dysfunction of the Thalamus. Like the cerebellum, the amygdala and hippocampus were enlarged in children with ASD as compared with control subjects, whereas no differences were found in adolescent amygdala volumes (Sparks et al., 2002; Schumann et al., 2004). In contrast, atrophy and reduction of serotonin transporter binding in the thalamus were reported in ASD from late childhood to adulthood (Tsatsanis et al., 2003; Hardan et al., 2006; Nakamura et al., 2010; Tamura et al., 2010). Higher microglial activity is found in the thalamus of ASD adults (Suzuki et al., 2013). From these results, it is presumed that in young children with ASD, neuroinflammation is initially induced in the thalamus, and, subsequently, persistent neuroinflammation induces thalamic atrophy in schoolchildren, adolescent, and adults. Because the thalamus neighbors the third ventricle, dysfunction of the thalamus in ASD may be related to impaired cellular metal homeostasis and BCB disruption (Sisó et al., 2010).

The thalamus plays a key role in sensory gate (Geyer and Vollenweider, 2008). Both auditory and visual stimuli from peripheral organs are sent to the thalamus, and then to the primary auditory or visual area in the cerebral cortex (Tamietto and de Gelder, 2010; Hackett, 2015). Functions of the thalamus are impaired in ASD schoolchildren, adolescents, and adults (Hardan et al., 2008; Lai et al., 2010). Significant decreases in cerebellar activity and cerebellum-thalamus connectivity are induced in a light or mild motor performance such as 20 finger taps for each hand in ASD schoolchildren (Mostofsky et al., 2009). In contrast, ASD individuals show significantly increased activity in the cerebellum relative to control subjects when they perform a rather complex motor task, in which they hold a joystick and press a button with the thumb according to instruction (Allen et al., 2004). From these results, it is likely that, in ASD, neural network activities between the cerebellum and thalamus are decreased at resting state, whereas this pathway is activated when a task is provided. In daily life of ASD individuals, activities of the cerebellum and cerebellum-thalamus pathway appear to be increased because social communication is always necessary.

Aberration of Verbal Communication. Underconnectivity in the thalamo-frontal pathway is induced in ASD schoolchildren and adolescents (Cheon et al., 2011). In contrast, functional overconnectivity between the thalamus and temporal lobe occurs in ASD schoolchildren and adolescents, although underconnectivity is found for other cortical regions (Nair et al., 2013). Therefore, it is possible that hyperactivation of the thalamus-temporal lobe connections is due to thalamo-frontal underconnectivity, and that dysconnectivity of these pathways is associated with ASD symptoms.

ASD adults fail to activate the superior temporal sulcus (STS)/superior temporal gyrus (STG) in response to human vocal sounds, whereas they show a normal activation pattern in response to nonvocal sounds (Gervais et al., 2004). Underconnectivity is induced between the STS/STG and dopaminergic reward pathway, including the ventral tegmental area and nucleus accumbens in ASD schoolchildren (Abrams et al., 2013). These results suggest that chronic hyperactivation of the thalamus-temporal lobe connections induces desensitization of the STS/STG, and that underconnectivity of STS/STG-reward pathway impairs the ability of ASD children to experience speech as a pleasurable stimulus, subsequently leading to deterioration of language and social skills. It is possible that the definite reduction of STS/STG reactivity to human vocal sounds in ASD is caused by disturbances of the prefrontal cortex, which regulates functions of the STS/STG and is implicated in social cognition.

There are neuronal connections between the STS/STG and ventrolateral prefrontal cortex (VLPFC) that integrate social cognitive information (Takahashi et al., 2007; Levy and Wagner, 2011; Lai et al., 2012). Underconnectivity between the temporal cortex and VLPFC occurs in adult ASD (Sato et al., 2012). In addition, VLPFC activity is significantly reduced in schoolchildren and adolescents with ASD relative to controls during speech stimulation (Lai et al., 2012). Accordingly, it is probable that in daily life of ASD children, cerebellar and thalamic hyperactivation induces dysfunction of the STS/STG and VLPFC, leading to a failure to integrate verbal information, which probably persists in adulthood.

Aberration of Nonverbal Communication. The thalamus, fusiform face area (FFA), STS/STG, and VLPFC also play a pivotal role in nonverbal communication, including facial expressions, gestures, eye contact, and body language (Redcay, 2008; Sato et al., 2012). These visual signals from the thalamus are sent to the visual cortex and FFA (Tamietto and de Gelder, 2010; Blank et al., 2011). Microglial activity is increased in the visual cortex/FFA of ASD individuals (Tetreault et al., 2012; Suzuki et al., 2013). Therefore, it is probable that thalamic hyperactivation induces microglia-mediated neuroinflammation and aberration of the visual cortex and FFA.

There are neuronal connections between the visual cortex/FFA, STS/STG, and VLPFC (Kreibel et al., 2007; Blank et al., 2011; Sato et al., 2012). The STS/STG plays a key role in direct structural connections between verbal- and nonverbal-recognition areas (Kreibel et al., 2007; Blank et al., 2011). Functional underconnectivity between the visual cortex and STS/STG or VLPFC occurs in ASD adults in response to emotional stimuli (Sato et al., 2012; Khan et al., 2013). Taken together, we hypothesize that abnormalities of verbal and nonverbal communication in ASD are due to cerebellar and thalamic hyperactivation and subsequent dysfunction of the visual cortex, FFA, STS/STG, and VLPFC.

Hippocampus-Amgydala Interaction and Emotional Responses. The hippocampus is thought to be vulnerable to developmental aberration during prenatal stage (Abernethy et al., 2002; Beauchamp et al., 2008). BCB abnormalities accompanying with impaired cellular metal homeostasis may be related to hippocampal dysfunction because of neighboring the hippocampus and lateral ventricle (Dziegielew ska et al., 2001; Kiernan, 2012).

The reciprocal interaction between amygdala and hippocampus contributes to emotion, emotion-related memory, and neurocognition, etc. (Potschka et al., 2011; Orsini and Maren, 2012). Hyperactivation of the amygdala occurs in ASD adults during identification of previously viewed faces (Kleinhaus et al., 2008; Monk et al., 2010; Dichter, 2012). Social impairment is positively correlated to amygdala activation but is negatively related to amygdala-FFA connectivity in ASD (Kleinhaus et al., 2008; Dichter, 2012). Development of face perception and social cognitive skills is supported by the amygdala-FFA system (Schultz, 2005; Vuilleumier and Pourtois, 2007). Therefore, underconnectivity of amygdala-FFA pathway in ASD appears to induce overconnectivity between the amygdala and brain regions other than FFA.

The ventromedial prefrontal cortex (VMPFC) plays a critical role in regulation of amygdala activity (Blair, 2013;
Motzkin et al., 2015). ASD subjects show increased neuronal activities in the VMPFC and amygdala in response to emotional stimuli and higher microglial activity in the VMPFC (Monk et al., 2010; Suzuki et al., 2013). Poor performance on the Iowa gambling task is found in ASD schoolchildren and adolescents, suggesting lower VMPFC functions (Sawa et al., 2013). Accordingly, it is likely that long-lasting hyperactivation of the amygdala induces VMPFC dysfunction, which is mediated by neuroinflammation. The dysfunction of VMPFC probably causes dysregulation between the VMPFC and amygdala and may induce aberration of emotional responses in ASD.

The DLPFC and Top-Down Control. Top-down control of lower brain regions by the DLPFC enables us to make appropriate planning and action in social situations based on integration of information, including verbal and non-verbal cognition, working memory, and evaluation of immediate as well as future outcomes (Tanaka et al., 2004; Weissman et al., 2008; Heatherton and Wagner, 2011). The number and size of neuron are significantly increased in the DLPFC of ASD subjects (Courchesne et al., 2011). Compared with typically developing subjects, ASD schoolchildren and adolescents perform significantly worse on DLPFC task (Dawson et al., 1998; Sawa et al., 2013). The ratio of N-acetyl-aspartate/creatine/phosphocreatine in the DLPFC is positively correlated with social ability scores in ASD children and adolescents (Fuji et al., 2010). From these results, hypoactivation of the DLPFC appears to occur in ASD like other psychiatric disorders (Hassel et al., 2008; Kang et al., 2012; Palaniyappan et al., 2013), and disturbances in top-down control of lower brain regions by DLPFC may result in social cognitive deficits.

Taken together, we hypothesize that impaired cellular metal homeostasis, one of the primary culprits, can initially induce disturbances of the BCB rather than BBB and subsequent cerebellar hyperactivation in young children with ASD. The cerebellar hyperactivation appears to increase thalamic activity and connectivity between the thalamus and STS/STG because of underconnectivity of the thalamo-frontal pathway, thereby resulting in dysfunction of STS/STG and VLPFC. In contrast, hyperactivation of the hippocampus and amygdala probably causes dysregulation of VMPFC responsible for emotional responses. These events in childhood may induce hypoactivation of the DLPFC, which controls lower brain regions related to social ability, and then lead to social cognitive deficits in ASD.

Social Cognitive Deficits in Schizophrenia

The major clinical, biochemical, and genetic features in ASD and schizophrenia are summarized in Table 1. Although contribution of pathogenic genes is different in these disorders, similar characteristics are seen in social cognitive deficits; disturbances in glutamate, γ-aminobutyric acid, and dopamine neurotransmission; and increasing proinflammatory responses.

Dysfunction of the Hippocampus and Amygdala. Findings concerning cerebellar aberration have been controversial in schizophrenia, unlike ASD (Bottmer et al., 2005). In schizophrenia, cerebellar disturbances contribute to neurological soft signs, such as observable defects in sensory integration, motor coordination, and behavioral inhibition, which are largely distinct from the core symptoms (Bottmer et al., 2005; Chan et al., 2010; Shinn, et al., 2015). Accordingly, it is unlikely that cerebellar aberration is associated with cognitive deficits in schizophrenia.

Individuals with at-risk mental state and patients with the first-episode or chronic schizophrenia have lower volumes of several brain regions including the hippocampus persistently

<table>
<thead>
<tr>
<th>TABLE 1</th>
<th>Comparison of clinical, biochemical, and genetic characteristics between ASD and schizophrenia</th>
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<tr>
<td><strong>ASD</strong></td>
<td><strong>Schizophrenia</strong></td>
</tr>
<tr>
<td>Clinical</td>
<td>Behavioral flexibility, delay of language, social cognitive deficits.⁎⁎&lt;br&gt;Worse performance than schizophrenia children in the theory of mind task.⁎&lt;br&gt;Manifests in early childhood.⁎</td>
</tr>
<tr>
<td>Biochemical</td>
<td>Disturbances in glutamate, GABA, and dopamine neurotransmission.⁎&lt;br&gt;Increases in proinflammatory cytokine (IL-1β, IL-6, TNF-α, IFN-γ) levels in the brain, CSF, and blood.⁎&lt;br&gt;No alterations in anti-inflammatory cytokine (IL-4, IL-10) levels in the blood.⁎</td>
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<tr>
<td>Genetic</td>
<td>CNTNAP2, NLGN, NRXN, SHANK3, CADM1, etc.†</td>
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<tr>
<td>Clinical</td>
<td>Positive, negative, cognitive symptoms (social cognitive deficits).⁶&lt;br&gt;Develops in late adolescence most frequently.⁶</td>
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<tr>
<td>Biochemical</td>
<td>Disturbances in glutamate, GABA, and dopamine neurotransmission.⁶&lt;br&gt;Increases in proinflammatory cytokine (IL-1β, IL-6, TNF-α) levels in the brain, CSF, and blood.⁶&lt;br&gt;Reduction of anti-inflammatory cytokine (IL-10, IL-13) levels in the CSF and blood.⁶</td>
</tr>
<tr>
<td>Genetic</td>
<td>DISC1, DTNBP1, NRG1, DRD2, HTR2A, COMT, etc.†</td>
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†Volkmann et al., 2014.<br>‡Pilowsky et al., 2000.<br>⁎Money and Stanwood, 2013.<br>⁴Onore et al., 2012.<br>⁵Ashwood et al., 2011b.<br>⁶Bourgeron, 2009.<br>⁷Stahl, 2013.<br>⁸Meyer et al., 2011b.<br>⁹Gejman et al., 2010.
In addition, significantly reduced hippocampal volume with relatively higher plasma IL-6 levels is induced in antipsychotic-naive schizophrenia patients with polymorphism IL-6 gene, implying that hippocampal aberration caused by elevated IL-6 is the neurodevelopmental origin of schizophrenia (Kalmady et al., 2014). Similarly, higher IL-6 response by maternal immune activation in prenatal stage is suggested to be associated with brain alterations to initiate schizophrenia (Brown, 2011). Therefore, the hippocampus appears to be a possible brain region to initiate schizophrenia.

The onset of psychosis is frequently preceded by weeks, months, or years of prodromal symptoms, including deficits in social cognitive functions. The cerebellum appears to play a predominant role in cognitive functions at young childhood because the cerebellum has fully matured at that time. In contrast, the prefrontal cortex is thought to contribute to cognitive functions along with its maturation progressively.

Fig. 2. A possible mechanism underlying social cognitive deficits in ASD and schizophrenia on their distinct ages of onset. (A) Social cognitive functions develop accompanying with human brain maturation from childhood to adulthood and are related to increases in myelination of white matter tracts between the prefrontal cortex and other brain regions. (B) In ASD, impaired cellular metal homeostasis, one of the primary culprits, can induce dysfunction of the BCB rather than BBB, thereby leading to cerebellar aberration and subsequent thalamic hyperactivation in childhood. In the next step, the overconnectivity is induced between the thalamus and temporal lobe (STS/STG) because of underconnectivity of the thalamo-frontal pathway. The thalamic hyperactivation is thought to be induced by microglia-mediated neuroinflammation and presumably leads to dysfunction of the prefrontal cortex, including DLPFC, which regulates functions of lower brain regions contributing to social cognition. In schizophrenia, in contrast, hippocampal aberration can occur in childhood and result in succeeding hyperactivation of the thalamus in late adolescence. The thalamic hyperactivation appears to be promoted due to immaturity of the fronto-temporal pathway and finally leads to DLPFC dysfunction with a similarity to ASD. (C) The cerebellum and prefrontal cortex are involved differently in social cognitive functions based on the maturation of the brain. The cerebellum appears to play a predominant role in cognitive functions at young childhood because the cerebellum has fully matured at that time. In contrast, the prefrontal cortex is thought to contribute to cognitive functions along with its maturation progressively.
perception, emotion, neurocognition, communication, and sleep (Larson et al., 2010). Individuals who later fulfilled diagnostic criteria for schizophrenia had shown significant premorbid deficits in intellectual, language, and behavioral abilities at the ages of 16–17 (Reichenberg et al., 2002). Symptoms such as problems of language and cognitive development in children (3–11 years old) can predict schizophreniform disorder in adults (Cannon et al., 2002). From these results, it is presumed that disturbances of hippocampus and related brain regions play a central role in prodromal symptoms of schizophrenia.

Schizophrenia patients show hyperactivation of the amygdala and underconnectivity of the VMPFC-amygdala pathway (Fan et al., 2013; Pankow et al., 2013). Therefore, it is probable that in schizophrenia, like ASD, increased activity in the amygdala caused by hippocampal hyperactivation induces desensitization and dysregulation of the VMPFC. These impairments of the VMPFC presumably lead to disturbances of emotional responses in prodromal period of schizophrenia.

**Dysfunction of the Thalamus, Temporal Cortex, and Prefrontal Cortex.** There is neuronal connectivity between the hippocampus and thalamus (Aggleton et al., 2010). The thalamus is one of the damaged brain regions in at-risk mental state individuals and schizophrenia patients (Borgwardt et al., 2007; Chan et al., 2011). Schizophrenia patients with thalamic dysfunction show spindle range deficits that may probably contribute to cognitive impairments (Ferrarelli et al., 2010; Wilson and Argyropoulos, 2012). In contrast, in healthy subjects, the fronto-temporal (VLPFC-STS/STG) connections reach 90% development in adulthood (Lebel et al., 2008), implying that immaturity of this pathway can prevent brain development in adolescence. Therefore, it is presumed that abnormalities of the thalamus caused by hippocampal hyperactivity can be exacerbated under immaturity of the fronto-temporal connections during late adolescence and early adulthood in schizophrenia. These disturbances can induce STS/STG desensitization and VLPFC dysfunction, thereby leading to disturbances of DLPFC top-down control (Fig. 2; Table 2).

**Cuprizone-Treated Mice as an Animal Model of Psychiatric Disorders**

The treatment with cuprizone [bis(cyclohexylidenehydrazide)], the copper chelator, severely alters copper and zinc homeostasis in various tissues, including the CNS, and induces demyelination in white and gray matters, such as the corpus callosum, cerebral cortex, hippocampus, and cerebellum in mice (Zatta et al., 2005; Groebe et al., 2009; Gudi et al., 2009; Koutsoudaki et al., 2009). The treatment of cuprizone in mice is thought to be useful as a model of prion infection because of the involvement of metal homeostasis in functions of a cellular prion protein (PrPc) (Martins et al., 2001). PrPc is predominately expressed in neuronal cells (Ramasamy et al., 2003) and can bind copper, zinc, iron, and manganese (Brazier et al., 2008; Davies et al., 2009). Interestingly, manganese can induce prion protein transformation from PrPc to a disease-associated isoform (PrPSc) (Brazier et al., 2008). Furthermore, PrPc but not PrPSc has SOD-1 activity,

### Table 2

<table>
<thead>
<tr>
<th>Brain Regions</th>
<th>Social Cognitive Functions</th>
</tr>
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<tbody>
<tr>
<td>Prefrontal cortex</td>
<td>Top-down control of social behavior</td>
</tr>
<tr>
<td>DLPC&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Integration of verbal and nonverbal information</td>
</tr>
<tr>
<td>VLPC&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Regulation for emotional responses</td>
</tr>
<tr>
<td>VMPFC&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Integration of auditory and visual perception</td>
</tr>
<tr>
<td>Thalamus&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Sensory gate for auditory and visual stimuli</td>
</tr>
<tr>
<td>Hippocampus&lt;sup&gt;e&lt;/sup&gt;</td>
<td>Emotion-associated memory, neurocognition</td>
</tr>
<tr>
<td>Amygdala&lt;sup&gt;f&lt;/sup&gt;</td>
<td>Emotional responses</td>
</tr>
<tr>
<td>Cerebellum&lt;sup&gt;g&lt;/sup&gt;</td>
<td>Cognition (early childhood), body and limb movement</td>
</tr>
</tbody>
</table>

<sup>a</sup>Heatherton and Wagner, 2011.
<sup>b</sup>Levy and Wagner, 2011.
<sup>c</sup>Motzkin et al., 2015.
<sup>d</sup>Kreiflets et al., 2007.
<sup>e</sup>Geyer and Vollenweider, 2008.
<sup>f</sup>Orsini and Maren, 2012.
<sup>g</sup>Wang et al., 2014.

![Fig. 3. Neuroinflammation in cuprizone-treated mice](https://jpet.aspetjournals.org)
indicating a high oxidation potential of PrPSc (Brown et al., 1999; Milhavet et al., 2000; Yamamoto and Kuwata, 2009). Therefore, the lacking of SOD-1 activity in PrPSc seems to be associated with reactive oxygen species production and neuroinflammation under impaired cellular metal homeostasis.

In C57BL/6 mice treated with cuprizone, the mRNA levels of CCL2, CCL5, and CXC-chemokine ligand 10 (CXCL10), alternatively termed IFN-γ-inducible protein 10, showed the greatest expression in the brain at 1–2 weeks of treatment, whereas CCL3, CCL4, tumor necrosis factor-α, and IL-1β increased later (4–5 weeks) (McMahon et al., 2001). Furthermore, activation of microglia and infiltration of macrophages into the brain are markedly increased during cuprizone intoxication (McMahon et al., 2002). Recently, it has been reported that microglial activation is significantly reduced in CXCL10-deficient mice treated with cuprizone, suggesting a pivotal role of CXCL10 in cuprizone-induced neuroinflammation and demyelination (Clarner et al., 2015). Similarly, IFN-γ, IL-6, IL-8, CCL4, and CXCL10 were shown to be significantly increased in the CSF of ASD individuals (Vargas et al., 2005). Consequently, impaired cellular metal homeostasis appears to induce neuroinflammation and demyelination mediated by M1 phenotype of macrophage/microglia in cuprizone-treated mice (Fig. 3).

Pharmacological Approach to Neuroinflammation in ASD and Schizophrenia

Because microglia-mediated neuroinflammation plays an important role in schizophrenia and ASD, a drug that suppresses microglial activation may be preferentially useful for the therapy of these disorders. One of such candidates is minocycline, which inhibits the polarization of proinflammatory M1 microglia (Kobayashi et al., 2013; Pusic et al., 2014). Minocycline is a second-generation tetracycline and has been in therapeutic use for over 30 years because of its antibiotic properties; however, it has been recently shown to exert a variety of biologic actions that are independent of their antimicrobial activity, including anti-inflammatory and anti-apoptotic activities (Garrido-Mesa et al., 2013).

Administration of minocycline attenuated the induction of M1 microglia markers and inhibited the upregulation of nuclear factor-κB, whereas it did not affect the expression of M2 microglia markers in cultured microglia stimulated with lipopolysaccharide and in the spinal cord of SOD-1/G93A mice (Kobayashi et al., 2013). In cuprizone-fed C57BL/6 mice, minocycline reduced microglial activation and demyelination in the brain and prevented disturbances in motor coordination (Pasquini et al., 2007; Skripuletz et al., 2010; Tanaka et al., 2013). Furthermore, minocycline in combination with an antipsychotic such as risperidone, olanzapine, quetiapine, or clozapine significantly improved positive, negative, and cognitive symptoms in recent-onset or chronic schizophrenia patients (Levkovitz et al., 2010; Ghanizadeh et al., 2014; Chaves et al., 2015; Kelly et al., 2015). From these results, it is likely that application of minocycline can dampen M1 signaling, subsequently resulting in skewing of M2a microglia that reduce proinflammatory signaling and increase production of anti-inflammatory cytokines. Consequently, minocycline add-on treatment may ameliorate clinical deterioration and brain alterations in schizophrenia patients.

Although there is no clinical use of minocycline in ASD, recent studies have revealed improvement of ASD symptoms by intranasal administration of oxytocin and demonstrated the association of polymorphisms in the oxytocin receptor (OXTR) gene in ASD (Andari et al., 2010; Guastella et al., 2010; Aoki et al., 2014; LoParo and Waldman, 2015). Furthermore, abnormal activation of microglia and a reduction of PSD-95 expression in the OXTR-deficient brain (Miyazaki et al., 2016) have been found. Prenatal minocycline treatment can alter the expression of PSD-95 and ameliorate abnormal mother-infant communication in OXTR-deficient mice (Miyazaki et al., 2016). These findings suggest that minocycline has a therapeutic potential for the development of oxytocin/OXTR-mediated ASD-like phenotypes.

Conclusion

In this review, we compare brain alterations in ASD and those in schizophrenia and propose a possible mechanism underlying social cognitive deficits. Development of ASD appears to be triggered by cerebellar dysfunction and subsequent thalamic hyperactivation in early childhood. In contrast, schizophrenia seems to be induced by thalamic hyperactivation in late adolescence, whereas hippocampal aberration possibly has been initiated in childhood. The thalamic hyperactivation can lead to dysfunction of the DLPFC, which regulates neural circuitry of social cognition. Consequently, we conclude that in ASD and schizophrenia, the initiating brain regions with abnormalities are distinct; however, the aberration of the same brain region contributes to social cognitive deficits, a common symptom. Furthermore, we strongly suggest that one of the primary culprits is a disturbance in metal homeostasis, which can induce dysfunction of the BCB rather than BBB. It is probable that dysfunction of CuZn SOD-1 expressed in the BCB leads to neuroinflammation via reactive oxygen species release, M1 polarization of macrophages/microglia, and production of proinflammatory cytokines. M1 microglia-mediated neuroinflammation appears to be associated with abnormalities of the initiating brain regions located adjacent to the cerebral ventricles and subsequent dysregulation of the neural circuitry of social cognition in the DLPFC. Consequently, a drug that selectively suppresses polarization of M1 microglia may provide a beneficial therapy for ASD and schizophrenia. From this point of view, cuprizone-treated mice are thought to be a useful model for metal homeostasis disturbance and neuroinflammation in these disorders. This view may pave the way for treatment of ASD and schizophrenia.

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Authorship Contributions

Wrote or contributed to the writing of the manuscript: Nakagawa, Chiba.

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