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A Potential Mechanistic Role for Neuroinflammation in Reward Processing Impairments in Autism Spectrum Disorder

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Abstract

Accumulating evidence suggests that autism spectrum disorder (ASD) may be conceptualized within a framework of reward processing impairments. The “Social Motivation Theory of Autism” posits that reduced motivation to interact with people and decreased pleasure derived from social interactions may derail typical social development and contribute to the emergence of core social communication deficits in ASD. Neuroinflammation may disrupt the development of mesolimbic dopaminergic systems that are critical for optimal functioning of social reward processing systems. This neuroinflammation-induced disturbance of mesolimbic dopaminergic functioning has been substantiated using maternal immune activation rodent models whose offspring show aberrant dopaminergic corticostriatal function as well as behavioral characteristics of ASD model systems. Preclinical findings are in turn supported by clinical evidence of increased mesolimbic neuroinflammatory responses in individuals with ASD. This review summarizes evidence for reward processing deficits and neuroinflammatory impairments in ASD and examines how immune inflammatory dysregulation may impair the development of dopaminergic mesolimbic circuitry in ASD. Finally, future research directions examining neuroinflammatory effects on reward processing in ASD are proposed.

Keywords

autism spectrum disorder; neuroinflammation; reward; dopamine

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Competing Interests

The authors declare that they have no competing interests.

1) Introduction

Autism spectrum disorder (ASD) is a highly heterogeneous neurodevelopmental disorder estimated to affect 1 in 59 children in the United States (Baio et al., 2018). Individuals with ASD present with extensive differences in symptom presentations, cognitive abilities, and adaptive skills. Given the heterogeneity inherent to the disorder, it is likely that multiple distinct etiological and pathophysiological factors contribute to the development of ASD. Despite the breadth of research investigating the developmental pathophysiology of ASD, no unifying etiological model has yet been established for ASD. This is in large part due to the intrinsic complexity of the genetics of ASD (Sahin & Sur, 2015), multiple environmental influences that have been shown to confer risk for ASD (Rossignol, Genuis, & Frye, 2014), and differential expression and identification of symptoms in males and females (Mandy & Lai, 2017) and children and adults (St Pourcain et al., 2017; Woodman, Smith, Greenberg, & Mailick, 2016) with ASD. These challenges associated with identifying a common etiologic factor for all individuals with ASD have impaired the development of novel psychosocial and pharmacological treatment options.

2) The Social Motivation Hypothesis of Autism

One approach to improved ASD treatment development is to consider mechanistic accounts that may apply to at least a significant subgroup of those with ASD who may share a common pathophysiology, thereby providing a mechanistic and functional framework for targeted treatment approaches suitable for that subgroup. Social communication impairments and their associated neurobiological underpinnings have received the majority of research attention as a path forward to understand ASD pathophysiology (Pelphrey, Shultz, Hudac, & Vander Wyk, 2011). Another candidate mechanism that has emerged recently are neurobiological systems associated with reward processing impairments in ASD. The framework that certain individuals with ASD are less motivated to interact with others and derive less pleasure from social interactions was introduced over a decade ago (Dawson, Webb, & McPartland, 2005), and this model has been useful for describing behavioral profiles and neural mechanisms of those individuals with ASD with decreased social motivational and pleasure responses (Chevallier, Kohls, Troiani, Brodkin, & Schultz, 2012; Dichter, Damiano, & Allen, 2012) as well as potential biomarkers for early emerging reduced social attention in ASD (Dawson, Bernier, & Ring, 2012).

The framework of the Social Motivation Hypothesis of Autism is that functional disruptions in brain circuits that support social motivation may constitute a primary deficit in ASD that may have downstream effects on the development of social cognition and communication (Chevallier, Kohls, et al., 2012; Kohls, Chevallier, Troiani, & Schultz, 2012). Decreased social motivation may not be the only mechanistic account of the full range of social deficits associated with ASD (e.g., some individuals with ASD have social interests and actively seek social interactions but fail to form friendships due to impaired social cognition and pragmatic language). However, even during the first year of life, infants with ASD demonstrate infrequent orienting to their own name and diminished eye contact (Ozonoff et al., 2010), suggesting that decreased social orienting and social interest are evident in

infancy in ASD and may interfere with the development of social cognition in at least a significant proportion of individuals with ASD (Dichter & Adolphs, 2012).

Social motivation is critical for optimal social development and learning (Fareri, Martin, & Delgado, 2008). During typical development, orienting to social stimuli begins in early infancy (Farroni, Massaccesi, Menon, & Johnson, 2007), including a neonatal preference for faces over non-face stimuli (Johnson, Dziurawiec, Ellis, & Morton, 1991). This prioritization is critical for social-communicative development (Brooks & Meltzoff, 2005) and social adaptation through the lifespan (Emery, 2000). Attention to social stimuli, even in infancy, is hypothesized to be accompanied by feelings of pleasure (Dawson et al., 2004), resulting in increased social motivation (Schultz, 2005) that promotes the development of neural systems underlying social information processing. In turn, such reward processing mechanisms may serve to encode and consolidate positive memories of social experiences that influence future responses to social stimuli and influence the development of brain systems that mediate social functioning more broadly (Chevallier, Kohls, et al., 2012).

Accordingly, the social impairments that characterize ASD may reflect decreased motivation to engage in reciprocal social behaviors in infancy and early childhood that would ultimately result in fewer experiences with social sources of information and decreased social learning (Dawson et al., 2005). When young children with ASD lack the motivation to participate in activities where social skills are typically forged, the resulting impoverished social environment further compounds social communication impairments and, thereby, negatively impacts the development of social cognition and social communication (Kuhl, Coffey-Corina, Padden, & Dawson, 2005; Schultz et al., 2000). Consistent with this model, very young children with ASD demonstrate decreased orienting to social stimuli (Dawson, Meltzoff, Osterling, & Rinaldi, 1998; Klin, Lin, Gorrindo, Ramsay, & Jones, 2009), and atypical social orienting has been shown to predict decreased social competence in adolescents with ASD (Klin, Jones, Schultz, Volkmar, & Cohen, 2002). There is also evidence that social motivation remains impaired in individuals with ASD despite growth in other areas of cognitive development. For instance, older children with ASD report experiencing less pleasure from social rewards (Chevallier, Grezes, Molesworth, Berthoz, & Happe, 2012) and social stimuli are less salient for individuals with ASD (Chawarska et al., 2014; Sasson et al., 2007). More generally, ASD is characterized by lower levels of reward responsivity (for review see Clements et al., 2018) and impaired reward-based learning (Johnson, Yechiam, Murphy, Queller, & Stout, 2006). Finally, intriguing preliminary findings that social communication abilities of individuals with ASD appear to improve under certain motivational contexts suggests that core social communication impairments in ASD may be influenced by motivational factors (Peterson, Slaughter, Peterson, & Premack, 2013).

3) Brain reward circuitry and motivated social behavior

The mesocorticolimbic dopamine system is the primary neural network responsible for reward processing behaviors including reward approach, reward receipt, and reward-based learning (Schultz, 2015). Reward processing is mediated by dense dopaminergic projections originating from the ventral tegmental area (VTA) that project to the striatum, orbitofrontal

cortex (OFC), ventromedial prefrontal cortex (vmPFC), and the anterior cingulate cortex, forming a mesolimbic dopamine pathway sensitive to the magnitude and probability of reward (Berridge, Robinson, & Aldridge, 2009; Schultz, 2000; Treadway & Zald, 2013). Reward-predictive dopamine bursts originating in VTA send signals to the striatum, including the nucleus accumbens (NAc), that mediate approach behaviors towards salient goals (Bjork & Hommer, 2007; Knutson & Cooper, 2005). Functioning of the mesocorticolimbic dopamine system can be assessed using a multitude of method, including dopamine levels, dopamine metabolite and precursor concentrations, and dopamine receptor binding activity.

The neural circuits that mediate reward processing may have evolved, at least in part, to facilitate social affiliation and attachment (Insel, 2003; Trezza, Damsteegt, Achterberg, & Vanderschuren, 2011). The ascending mesolimbic dopamine system mediates responses to social and nonsocial incentives (Gunaydin & Deisseroth, 2014) and dopamine transmission in the nucleus accumbens modulates social play behaviors (Manduca et al., 2016). Social interaction mobilizes the same mesolimbic network that is active during the processing of nonsocial rewards such as food, money, and drugs of addiction (Schultz, 1997; Zink, Pagnoni, Martin-Skurski, Chappelow, & Berns, 2004). Further, functioning of the mesolimbic circuit in the context of rewarding stimuli is associated with high valuation, incentive salience, and motivation (Smith, Berridge, & Aldridge, 2011). Therefore, reward mechanisms may serve to encode and consolidate positive memories of social experiences, facilitating social abilities hypothesized to be impaired in ASD (Chevallier, Kohls, et al., 2012).

4) Dopaminergic Impairments in ASD

A. Preclinical Evidence

Preclinical and clinical findings suggest that impaired mesolimbic dopamine functioning may contribute to cardinal features of ASD (Dichter & Adolphs, 2012; Hara et al., 2015; Staal, 2015). For example, the valproic acid model of ASD is one of the most widely used ASD animal models (Mabunga, Gonzales, Kim, Kim, & Shin, 2015); prenatal valproic acid exposure causes ASD-like phenotypes and a cascade of neurobiological changes, including excitatory/inhibitory neural imbalances linked to increased basal dopamine in the frontal cortex (Narita et al., 2002), hyperactive mesocortical dopamine in response to stress (Nakasato et al., 2008), and changes in locomotor behavior akin to that observed in striatal dopamine-depleted animals (Shaywitz, Yager, & Klopper, 1976). Additionally, *SHANK3* has been proposed as candidate gene for ASD (Durand et al., 2007; Pinto et al., 2010). *SHANK3* is expressed in the VTA, and manipulations that reduce social interaction, such as social defeat stress, lead to significant reductions in VTA *SHANK3* expression (Warren et al., 2013). In mice, disruption of *SHANK3* leads to impaired social reward phenotypes (Wang et al., 2011). Additionally, SHANK3 impairs the maturation of excitatory synapses onto VTA dopamine neurons and results in reduced *in vivo* burst activity of dopamine neurons. Further, optogenetic activation of VTA dopamine neurons increases social preference in SHANK3-deficient mice, linking sufficiency of dopamine neuron activity to social interaction functions (Bariselli et al., 2016).

B. Clinical Evidence

Clinically, there is evidence of impaired mesolimbic functioning in ASD. Individuals with ASD demonstrate altered effort-based decision making for rewards (Damiano, Aloi, Treadway, Bodfish, & Dichter, 2012; Mosner et al., 2017; Watson et al., 2015). Recent findings also show that individuals with ASD experience difficulty in social reward-based learning (Li et al., 2017). Additionally, social communicative abilities may improve in ASD under optimal motivational conditions (Chevallier, Kohls, et al., 2012; Lahaie et al., 2006; Wang, Dapretto, Hariri, Sigman, & Bookheimer, 2004). For instance, Peterson and colleagues (2013) demonstrated that adequate incentives boosted motivation and, as a result, improved performance on a theory-of-mind task in children with ASD.

Common polymorphisms of the dopamine D4 receptor gene and the dopamine transporter gene are related to challenging behaviors (Gadow, Devincent, Olvet, Pisarevskaya, & Hatchwell, 2010) and repetitive behaviors (Gadow, DeVincent, Pisarevskaya, et al., 2010) in ASD, and linkages have been reported between polymorphisms of the dopamine-3-receptor gene and striatal volumes (Staal, Langen, van Dijk, Mensen, & Durston, 2015) as well as symptoms of repetitive behaviors (Staal, 2015) in ASD. Oxytocinergic abnormalities in ASD (Bell, Nicholson, Mulder, Luty, & Joyce, 2006; Depue & Morrone-Strupinsky, 2005; Dolen, 2015; Ross, Cole, et al., 2009) and initial reports of the therapeutic effects of intranasal oxytocin administration for treating core ASD symptoms (Andari et al., 2010; Guastella et al., 2010; Guastella, Mitchell, & Dadds, 2008) suggest an etiologically-relevant role for mesolimbic dopamine functioning in ASD. Although oxytocin impacts multiple systems, there are dense oxytocin projections within the mesolimbic dopamine system, including oxytocin neurons that project to both the ventral tegmental area and the nucleus accumbens (Ferguson, Young, & Insel, 2002; Insel & Young, 2001; Ross, Freeman, et al., 2009), and oxytocin receptor activation plays an important role in the activation of reward pathways during pro-social behaviors, suggesting that oxytocin may improve social symptoms in ASD via effects on the mesolimbic dopamine system (Choe et al., 2015; Dolen, Darvishzadeh, Huang, & Malenka, 2013; Olazabal & Young, 2006).

Perhaps the strongest evidence for reward-sensitive mesolimbic impairment in ASD stems from functional neuroimaging studies (for review see Clements et al., 2018). These studies have generally, but not always, found striatal hypoactivation in individuals with ASD during the processing of monetary rewards in the context of incentive delay tasks (Delmonte et al., 2012; Dichter, Felder, et al., 2012; Dichter, Richey, Rittenberg, Sabatino, & Bodfish, 2012) as well as a range of other non-reward cognitive tasks (Carlisi et al., 2017; Choi et al., 2015; Kohls et al., 2013; Schmitz et al., 2008; Scott-Van Zeeland, Dapretto, Ghahremani, Poldrack, & Bookheimer, 2010; Solomon et al., 2015). Further, there is evidence for functional mesolimbic impairments in response to social rewards (Delmonte et al., 2012; Dichter, Felder, et al., 2012; Scott-Van Zeeland et al., 2010) and negative social reinforcements (Damiano et al., 2015) in ASD. It is noteworthy that functional mesolimbic impairments are evident in response to a range of rewards, including responses to food cues (Cascio et al., 2012) and special interests (Cascio et al., 2014; Dichter, Felder, et al., 2012), highlighting that functional mesolimbic impairments in ASD may not be specific to social

stimuli but may extend more broadly to range of rewarding stimuli (Dichter & Adolphs, 2012).

5) Neuroinflammation as a Mechanistic Account of Reward Processing Impairments in ASD

The remainder of this review presents evidence that ASD is characterized by aberrant neuroinflammatory processes and that these processes represent a mechanistic factor contributing to the development and maintenance of reward processing impairments in ASD via effects on mesocorticolimbic dopamine systems. There is evidence to suggest a negative relationship between neuroinflammatory response and dopamine signaling via different pathways and receptors (i.e., D1, D2, D3). Specifically, decreases in dopaminergic activity have been linked with increased levels of inflammatory markers (Yan et al., 2015), while heightened dopamine responses are associated with attenuated cell-death as a result of immunological insult (e.g., lipopolysaccharide (LPS); Iravani et al., 2008). While dopaminergic signaling clearly impacts immunological responses, this review will largely provide evidence of the immunological effects on dopamine and its metabolites. These distinct perspectives may, in fact, reflect a bidirectional association between dopamine reactivity and inflammation. Linkages between neuroinflammation and mesocorticolimbic dopamine function have been previously described in the context of other psychiatric conditions (e.g., depression and anhedonia; Felger & Treadway, 2017) and neurodegenerative disorders (e.g., Parkinson's disease; Kaur, Gill, Bansal, & Deshmukh, 2017), and there is emerging preclinical and clinical data that comparable linkages may be characteristic of ASD as well.

6) Overview of the Immune System

The immune system is a complex defense mechanism that serves to protect an organism from potentially harmful pathogens via innate and adaptive systems (see Parkin & Cohen, 2001 for a review). The innate immune system is a nonspecific first line of defense against antigens and includes physical barriers such as the skin, chemical barriers within the blood (e.g., antimicrobial proteins), and cells that attack potentially harmful foreign bodies. Cells involved within the innate system include neutrophils, dendritic cells, natural killer cells, mast cells, monocytes, and macrophages. Resident brain macrophages, known as microglia, serve a maintenance function by aiding in synaptic maturation and phagocytosis, a process by which pathogens or cell debris are degraded and destroyed (Takano, 2015). Microglia and other macrophages are also responsible for releasing cell-signaling molecules (i.e., cytokines) when activated by immunological insults. Cytokines, including interferons (e.g., IFN-α) and interleukins (e.g., IL-6, IL-1β), regulate pro- and anti-inflammatory responses and facilitate communication between the innate and adaptive arms of the immune system (Masi, Glozier, Dale, & Guastella, 2017). Adaptive immunity is then triggered when innate immunity is unable to ward off a pathogen, and this branch of the immune system is comprised of white blood cells, called B cells and T cells. In addition, the adaptive system serves a memory function for subsequent pathogen activations. Together, the innate and

adaptive immune systems engage in complex communications with one another to maintain a defense against foreign and native threats (Filiano, Gadani, & Kipnis, 2015).

7) Effects of Neuroinflammation on Reward Processing

A. Preclinical Studies

The link between neuroinflammation and dopamine dysregulation has been explored in numerous studies using a variety of stimuli (e.g., interferon-alpha, IFN-α, endotoxin) known to induce systemic inflammatory responses. Shuto, Kataoka, Horikawa, Fujihara, and Oishi (1997) first observed significantly depleted dopamine levels in cytokine-treated mice compared to mice treated with saline. More recently, studies examining the offspring of immune-challenged rodents have reported significant dopamine disruptions in canonical reward processing brain regions (Kirsten, Taricano, Flório, Palermo-Neto, & Bernardi, 2010; Vuillermot, Weber, Feldon, & Meyer, 2010). Further, animals exposed to inflammatory stimuli have also shown behavioral impairments, such as decreased motivation to work for food (Felger et al., 2013; Nunes et al., 2014), inhibited environmental exploring (Felger et al., 2007), and decreased sexual motivation (Bernardi et al., 2010). Using positron emission tomography (PET) imaging, which allows for the examination of metabolic and neurochemical changes in the brain, Felger and colleagues (2013) observed reductions in dorsal striatal dopamine release following chronic IFN-α administration in rhesus monkeys. Similarly, single administrations of IFN-α in rats resulted in reduced striatal dihydroxphenylacetic acid (DOPAC), a metabolite of dopamine (Kamata, Higuchi, Yoshimoto, Yoshida, & Shimizu, 2000; Sato et al., 2006). IFN-α administration in rats has also been associated with decreased dopamine within the amygdala and raphe nucleus (Kitagami et al., 2003). Together, these findings demonstrate the potential for inflammatory responses to downregulate neural dopamine in preclinical samples. However, some rodent studies have also reported increases in neural dopamine following IFN-α administration (Kumai et al., 2000; Sato et al., 2006), and Felger and Miller (2012) suggest that this discrepancy within the preclinical literature may reflect differences in cytokine dosing and length of exposure. Overall, these preclinical findings contribute to a model of inflammation-induced disruption of corticostriatal dopamine pathways.

B. Clinical Studies

Consistent with preclinical evidence, human fMRI studies investigating the impact of inflammation on the brain have also shown distinct effects on dopaminergic neural circuitry (Capuron et al., 2007; Capuron et al., 2012; Dowell et al., 2016; Eisenberger et al., 2010; Felger et al., 2013). For example, experimentally-induced inflammation has been shown to attenuate ventral striatal activation in response to reward tasks (Capuron et al., 2012; Eisenberger et al., 2010). Healthy individuals exposed to a single administration of low-dose endotoxin showed significantly attenuated neural activation within the ventral striatum to monetary reward cues relative to placebo-treated controls (Eisenberger et al., 2010). Typhoid vaccination, which evokes a brief inflammatory response, has also been associated with decreased ventral striatal response to reward prediction errors, as well as increased insula encoding of punishment prediction error, relative to placebo-treated controls (Harrison et al., 2016). Similarly, patients with chronic hepatitis C virus (HCV) receiving IFN-α treatment

showed diminished ventral striatal activation during a hedonic reward task compared to untreated patients (Capuron et al., 2012). Within this same study, attenuated ventral striatal activity was significantly correlated with patient reports of decreased motivation. However, in contrast to these findings of decreased striatal response to reward stimuli following an inflammatory challenge, there are reports of increased ventral striatal sensitivity to social rewards and social threats following endotoxin exposure (Inagaki et al., 2015; Muscatell et al., 2016). Consequently, Inagaki (2015) and Muscatell (2016) hypothesized that inflammation-induced neural responses may be highly sensitive to the context in which they are processed. These discrepancies highlight the need for future work to evaluate the effects of experimentally-induced inflammation on neural and behavioral responses to different classes of rewards.

Molecular neuroimaging has further clarified linkages between neuroinflammation and impaired mesolimbic dopamine circuitry functioning. For example, examinations of neurometabolic functioning in HCV patients following a three-month-long IFN-α treatment course revealed increased resting state glucose metabolism in dorsal striatal regions (Juengling et al., 2000). Based on findings from the Parkinson's disease literature, this hypermetabolic state is thought to reflect the loss of inhibitory dopamine neurons (Eidelberg et al., 1994; Mentis et al., 2002; Wichmann & DeLong, 1999). These findings have since been replicated and expanded upon by Capuron and colleagues (2007) using a sample of patients with malignant melanoma receiving IFN-α therapy over the course of four weeks: not only was dorsal striatal glucose metabolism enhanced following IFN-α treatment, but this effect was also significant within ventral striatal regions. Relatedly, Capuron and colleagues (2012) found that IFN-α therapy for patients with HCV resulted in increased uptake of dopamine neurotracer ^{18}F-Dopa and decreased ^{18}F-Dopa turnover within ventral and dorsal striatal regions, reflecting significant changes in presynaptic striatal dopamine function as a result of treatment. Specifically, these changes are indicative of decreased dopamine synthesis and release. Together these preclinical and clinical findings demonstrate the potential for inflammatory responses to alter dopaminergic activity within neural reward circuitry (see Figure 1), and thereby impact animal and human reward and motivational behavior.

Finally, some of the strongest documented links between immune dysfunction and reward-oriented behaviors have been illustrated in studies of individuals exposed to inflammatory stimuli (Eisenberger et al., 2010) or those undergoing immunotherapy to treat medical illness (Capuron et al., 2002; Capuron et al., 2012). Following an endogenous or experimentally-induced immune response, individuals in these studies have repeatedly exhibited symptoms collectively referred to as "sickness behavior". Sickness behavior is a set of vegetative, somatic, and psychological responses that are considered to be adaptive in recovery to illness (Dantzer, O'Connor, Freund, Johnson, & Kelley, 2008). Behavioral presentation is characterized by low appetite, fatigue, social withdrawal, and generally low motivation (Dantzer & Kelley, 2007). Following exposure to a single administration of low-dose endotoxin, Eisenberger et al. (2010) reported that healthy adult participants displayed significantly greater levels of sickness behavior compared to placebo-treated participants. These symptoms of sickness behaviors were also accompanied by increased endorsement of symptoms of depression and anhedonia, conditions that are characterized by and diagnosed

based on impaired responses to pleasure and decreased motivation (Nestler & Carlezon, 2006). These findings have been corroborated in patients receiving IFN-α treatments, who, compared to patients administered placebo medications, reported increased sickness behavior and depressed mood (Capuron et al., 2002; Capuron et al., 2007; Capuron et al., 2012).

8) Evidence of Neuroinflammation in ASD

A. Maternal Immune Activation and ASD Risk

Some of the strongest etiologic evidence of neuroinflammatory processes in ASD derive from studies of maternal immune activation (MIA). These studies highlight that immune dysregulation in ASD may be triggered as early as during fetal development by innate maternal antibodies, as well as maternal infection during pregnancy. Because the blood-brain barrier is increasingly permissive during gestation (Adinolfi, Beck, Haddad, & Seller, 1976), maternal immune cells are capable of accessing the developing fetal brain, making these developing neural networks more susceptible to harm (Karpiak & Rapport, 1975). Maternal infection during pregnancy has shown deleterious effects and hospital admissions to maternal viral infection in the first trimester or bacterial infection within the second trimester significantly increased the risk of offspring developing ASD (Atladóttir et al., 2010; Estes & McAllister, 2016). During maternal infection, children who go on to develop ASD may be exposed in utero to maternal anti-brain antibodies (Immunoglobulin G (IgG); Edmiston, Ashwood, & Van de Water, 2017). These antibodies appear to respond in a heightened manner to fetal brain tissue (i.e., fetal brain tissue is treated as a foreign pathogen), resulting in neurotoxic effects that increase the risk for developing ASD (Braunschweig & Van de Water, 2012; Zimmerman et al., 2007). Consistent with this framework, there are elevated rates of autoimmune disorders (e.g., Lupus, rheumatoid arthritis, celiac disease, hypothyroidism) in mothers of children with ASD (Comi, Zimmerman, Frye, Law, & Peeden, 1999; Keil et al., 2010), and children born to mothers with autoimmune disorders are 34% more likely to be diagnosed with ASD (Chen et al., 2016).

B. Autoimmune Anti-Brain Antibodies in ASD

Anti-brain antibodies are not only present in mothers of children with ASD but are also present in children and adults with ASD (Hoffmann et al., 2016). These anti-brain autoantibodies target a variety of neural components (Connolly et al., 1999; Singh, Singh, & Warren, 1997; Singh, Warren, Odell, Warren, & Cole, 1993) and are significantly more prominent in individuals with ASD (Goines et al., 2011; Wills et al., 2009). In addition, these antibodies appear to be most significantly elevated in ASD within brain regions associated with reward processing, including the dorsal striatum, prefrontal cortex (PFC) and anterior cingulate gyrus (ACG), as well as the cerebellum (Singer et al., 2006). In a study investigating the effects of human-derived serum antibodies on rodent brain proteins using immunoblotting with specific antigens for myelin basic protein and glial acidic fibrillary protein, Zimmerman and colleagues (2007) showed that sera from ASD children were significantly more reactive to rodent brain proteins than sera antibodies of unaffected siblings and their parents. This finding highlights the potentially neurotoxic effects of

human-derived serum antibodies. In some instances, these anti-brain antibodies have also been associated with more severe cognitive, motor, adaptive, language and developmental impairments in individuals with ASD (Piras et al., 2014).

C. Aberrant Cytokine Concentrations in ASD

Glial cells (i.e., astrocytes and microglia) provide structural support and nutrients for neurons and play a critical role in phagocytosis, and there is evidence of increased glial activation in ASD. Upregulated glial activation has been shown to be directly related to alterations in peripheral and central cytokine expression in ASD (for review see Masi et al., 2017; Masi et al., 2015). This aberrant cytokine profile in ASD is evidenced by both increased pro-inflammatory responses (Ashwood et al., 2011b; Chez, Dowling, Patel, Khanna, & Kominsky, 2007) and decreased anti-inflammatory responses (Ashwood et al., 2008; El Gohary, El Aziz, Darweesh, & Sadaa, 2015; Okada et al., 2007), contributing to a largely pro-inflammatory profile in ASD. Altered cytokine concentrations have been associated with more severe behavioral features of the disorder, including: increased stereotypies, greater impairments in communication and daily living skills, increased hyperactivity, and increased overall ASD symptom severity (Ashwood et al., 2012; Ashwood et al., 2011b; El Gohary et al., 2015; Piras et al., 2014), as well as greater nonverbal and verbal developmental disruption (Careaga et al., 2017). Ashwood and colleagues (2011b) reported significant differences in cytokine concentrations between individuals with ASD who did and who did not experience regression, such that children with regressive ASD exhibited increased cytokine levels relative to children with no history of regression. These findings have provided support for the use of immunological markers in exploring endophenotypic subtypes of ASD and suggest a heightened inflammatory environment in some individuals with the disorder (Bryn et al., 2017).

Finally, increased lethargy in individuals with ASD has been associated with increases in eotaxin, IL-8, and IL-12p40, whereas greater stereotypy has been associated with increases in eotaxin, IL-1β, IL-6, IL-8, and IL-12p40 (Ashwood et al., 2011a, 2011b). More severe nonverbal communication impairments in individuals with ASD have been linked with enhanced concentrations of IL-4 (Ashwood et al., 2011b). Finally, increased hyperactivity and worsened cognitive and adaptive ability in ASD have been shown to accompany increased IL-8 levels (Ashwood et al., 2011b). Individuals with ASD with heightened proinflammatory profiles displayed greater impairment in social affect, as well as cognitive, language, and motor development, compared to individuals with ASD with relatively attenuated proinflammatory profiles (Careaga et al., 2017).

9) Effect of Neuroinflammation on Reward Behaviors and Dopaminergic Circuitry in ASD

A. Preclinical Findings

There is a growing literature examining the effects of experimentally-induced neuroinflammation on reward-related behaviors and associated mesocorticolimbic brain dopamine function in preclinical models. However, there is inconsistency with respect to the directionality of this disruption, perhaps due at least in part to the specific immunological

stimuli administered. For example, both polyinosinic:polycytidylic acid (poly I:C) and lippopolysaccaride (LPS) have been administered to pregnant rodents to mimic viral and bacterial infections, respectively. Offspring of these immune-challenged mothers have repeatedly shown significant dysregulation in striatal and prefrontal brain regions, and they serve as ASD preclinical models of inflammation. Adult and peripubertal offspring of LPS-exposed rodents demonstrate consistently attenuated dopamine activity (measured by dopamine directly as well as its metabolites, DOPAC and homovanillic acid (HVA)) within striatal and thalamic brain regions (see Table 1; Kirsten & Bernardi, 2017; Kirsten, Taricano, Flório, et al., 2010; Soto et al., 2013). An exception to this trend includes a report of *increased* dopamine concentrations within the nucleus accumbens of adult rats born to LPS-exposed mothers (Romero, Guaza, Castellano, & Borrell, 2010). This same study reported a developmentally-mediated interaction between MIA and striatal dopamine levels such that peripubertal rats showed decreased striatal dopamine whereas adult rats showed increased striatal dopamine relative to saline-exposed offspring.

Alternatively, offspring of poly I:C-exposed rodents primarily show a more variable dopamine profile that appears to be developmentally mediated (see Table 1; Meyer, Engler, et al., 2008; Meyer, Nyffeler, et al., 2008; Ozawa et al., 2006; Vuillermot et al., 2010; Zuckerman et al., 2003). Much like peripubertal rodents exposed to bacterial LPS in utero, peripubertal rodents born to viral poly I:C-exposed mothers show decreased levels of dopamine markers, including diminished tyrosine hydroxylase (TH) and dopamine transporter (DAT) expression within the NAcc and dorsal striatum (Vuillermot et al., 2010). Respectively, these proteins are tasked with dopamine biosynthesis and reuptake (Daubner, Le, & Wang, 2011; Vaughan & Foster, 2013). Poly I:C-induced alterations in dopamine binding have also been observed, although findings are mixed. D_2 receptors in adult rodents downregulate binding in the striatum and PFC in response to prenatal poly I:C administration (Meyer, Nyffeler, et al., 2008; Ozawa et al., 2006) whereas the pattern for D_1 receptors is less uniform. Vuillermot and colleagues (2010) reported increased D_1 receptor binding within the dorsal striatum and the NAcc shell as a result of prenatal exposure to poly I:C, yet this pattern differed with previous findings that showed no difference between striatal D_1 binding in rodents exposed to poly I:C in utero (Ozawa et al., 2006). This discrepancy may be attributed to differences in dopamine receptor function, as each receptor projects its output to unique neural regions via distinct pathways. Broadly, it has been suggested that these receptors interact in both synergistic and opposing fashions (Keeler, Pretsell, & Robbins, 2014). In addition, these receptor-specific responses may reflect D_1 receptor tendencies to respond to phasic (i.e., more acute) dopamine activity, whereas D_2 is more sensitive to tonic (i.e., extended) dopamine release (Dreyer, Herrik, Berg, & Hounsgaard, 2010). The precise timing of the prenatal immunological insult may also account for the observed difference in dopamine receptor response. Specifically, immunological insults presented earlier in gestation may result in hyperactive striatal DA, whereas insults encountered later in pregnancy may be associated with hypoactive striatal dopamine (Meyer, Yee, & Feldon, 2007).

Additionally, prenatal endotoxin exposures lead to increased maternal inflammatory response and enhanced cytokine concentrations in the offspring of affected mothers. For example, adult offspring of immune-challenged rodents showed significantly greater serum

cytokines levels including: IL-1β, IL-2, IL-6, and TNF-α (Borrell, Vela, Arévalo-Martin, Molina-Holgado, & Guaza, 2002; Kirsten, Lippi, Bevilacqua, & Bernardi, 2013; Romero et al., 2010). This finding corroborates results describing increased inflammatory profiles in individuals with ASD and indicates that prenatal exposure to immunological insults may have lifelong impacts on neuroinflammatory profiles. Additionally, such inflammation-induced disruptions are associated with impairments in rodent social behaviors (Kirsten, Taricano, Maiorka, Palermo-Neto, & Bernardi, 2010) and restricted and repetitive behaviors, such as self-grooming (Kirsten & Bernardi, 2017). Discrepancies within the preclinical literature between broader neuroinflammation-induced dopamine dysregulation and ASD-specific immune activated models may reflect differences in the effect of MIA and post-natal immunological disruptions on dopamine function. It appears that the developmental stage in which the immunological disturbance occurs significantly influences the effect of distinct inflammatory stimuli on dopamine functioning. Although previous studies have noted significant impacts of direct LPS administration in adult rodents and adult offspring of LPS-treated mothers, it is unclear how these inflammation-induced dopamine disruptions differ from one another as a function of the timing of immunological insult (Dunn, 2006), highlighting the importance of a developmental framework to understand the impact of neuroinflammation on dopamine neural pathways.

B. Clinical Findings

Evidence of linkages between mesolimbic dopamine dysfunction and neuroinflammation in ASD is supported by the presence of anti-brain antibodies, heightened microglial activation, and increases in cytokine concentrations in mesocorticostriatal neural networks in ASD (see Table 2; Morgan et al., 2010; Singer et al., 2006; Vargas, Nascimbene, Krishnan, Zimmerman, & Pardo, 2005).

A study of 68 children with ASD and 30 typically developing children revealed that the serum from 49% of children with ASD contained anti-brain antibodies in the caudate nucleus, and another 18% of the ASD group had antibody-positive sera within the cerebral cortex, whereas no one within the TDC group presented with anti-brain antibodies within the caudate nucleus (Singh & Rivas, 2004). A study using western immunoblotting found increased serum antibodies in the caudate nucleus, putamen, and PFC in individuals with ASD (Singer et al., 2006), and subsequent enzyme-linked immunosorbent assay (ELISA) optical density readings replicated these findings within the putamen. Post-mortem studies have revealed evidence of hyperactive microglia and astroglia in ASD, a pattern that may lead to neuronal alternations mediated by the secretion of inflammatory cytokines. Vargas and colleagues (2005) described significant increases in anti-inflammatory cytokine tumor growth factor-β1 (TGF-β1) within the MFG, ACG, and white matter of the post-mortem brains of 11 individuals with ASD. Since this seminal finding, other studies have also reported increased microglial activation, as well as enhanced microglial volume, in the brain tissue of individuals with ASD (Morgan et al., 2012; Morgan et al., 2010; Suzuki et al., 2013). Other cytokines such as interleukin-10 (IL-10) and interleukin-6 (IL-6) are also increased in the ACG in individuals with ASD. Investigations of the broader cerebral cortices of individuals with ASD corroborated this finding of significantly enhanced IL-6 levels and also reported increased concentrations of tumor necrosis factor-α (TNF-α) and

interferon-γ (IFN-γ; Li et al., 2009). In some cases, immunocytochemical staining analyses have revealed the cellular sources of these cytokine increases. For example, IL-6 was shown to be prominently expressed within activated astrocytes in cortical, cerebellar and subcortical white matter regions, whereas TGF-β1 showed expressions within both activated microglia and astrocytes in cerebellar regions only (Vargas et al., 2005).

There is a single molecular imaging study assessing binding potential of the 18-kdopamine translocator protein (formerly peripheral benzodiazepine receptor), a putative measure of microglial activation during neuroinflammation, in ASD. Using ([11C](R)-PK11195 positron emission tomography (PET) imaging, Suzuki and colleagues (2013) reported hyperactive microglia in the ACG, MFG, and OFC in adults with ASD. Finally, though not a direct measure of neuroinflammation, it is noteworthy that two large-sample studies have reported elevated extra-axial cerebrospinal fluid in 6-24 month old infants who developed ASD in a manner that predicted the severity of ASD symptoms (Shen et al., 2017; Shen et al., 2013). Given the central role that extra-axial cerebrospinal fluid plays in beta-amyloid clearance (Xie et al., 2013), paravenous drainage of inflammatory cytokines (Iliff et al., 2012), and meningeal immune surveillance (Louveau et al., 2015), extra-axial cerebrospinal fluid elevations in infants who develop ASD is consistent with a neuroinflammatory model of ASD.

Taken together, we propose that neuroimmune dysregulations may contribute to the etiology and maintenance of ASD by preferentially disrupting mesocorticolimbic dopamine, and thereby impacting reward behaviors in individuals with the disorder. In addition, the preclinical work in this area suggests that this effect may be developmentally mediated.

10) Future Directions

Although research to date broadly supports that neuroinflammation impacts dopamine circuitry functioning in ASD, there are still important considerations that require further examination. First, few studies have used molecular imaging (i.e., PET and single-photon emission computed tomography (SPECT)) in ASD to directly measure dopamine functioning. FMRI studies in ASD have largely established a profile of underactive mesolimbic responses within corticostriatal areas to reward stimuli; however, little is known about dopamine and dopamine metabolite activity and binding in ASD (Zürcher, Bhanot, McDougle, & Hooker, 2015). Although the field has a breadth of preclinical work examining dopamine and its metabolites in ASD-models, this lack of clinical findings makes it difficult to compare results across mammalian samples. The few human studies that have examined dopamine and dopamine metabolite binding in ASD have reported results of both increased (Ernst, Zametkin, Matochik, Pascualvaca, & Cohen, 1997) and decreased (Nieminen-von Wendt et al., 2004) presynaptic dopamine activity in ASD within prefrontal cortical regions. This discrepancy may be attributed to methodological differences, including the use of anesthesia for sedation which decreases striatal dopamine release in preclinical models (Schulte et al., 2000). Similarly, mixed results have been reported regarding DAT binding in ASD. Results from PET and SPECT imaging studies have provided varied findings including increased DAT binding in OFC in ASD (Nakamura et al., 2010), as well as no significant differences (Makkonen, Riikonen, Kokki, Airaksinen, & Kuikka, 2008).

Future ASD molecular imaging studies will be needed to clarify the impact of neuroinflammation on dopamine functioning and behavior in individuals with ASD with emphasis on contextual and environmental factors that influence neuroinflammation.

In addition, PET and SPECT imaging may help to address some of the current limitations of post-mortem neuroinflammation studies. Although post-mortem analyses of inflammatory responses yield important findings across varied developmental and functional levels, these analyses are limited in their ability to connect these inflammatory profiles with behavioral functioning as they rely exclusively on retroactive reports of diagnoses and symptom expression. Metabolic imaging, on the other hand, allows researchers to link *in vivo* dopamine activity to current behavior. To date, many ASD post-mortem studies examining neuroinflammation have been limited in scope based on *a priori* regional brain hypotheses. Although there is clear evidence of enhanced neuroinflammatory profiles in cortical regions in ASD, only a small number of studies have examined neuroinflammation in the striatum and broader midbrain in ASD. In addition, it is difficult to disentangle whether the observed neuroimmunological state of post-mortem tissue represents a consequence of the disorder or an etiological factor contributing to the development of the condition.

Future research should also address the correspondence in ASD between peripheral measures concentrations of cytokine levels in serum or cerebrospinal fluid (CSF) and central measures of cytokine profiles. Findings from several studies have reported discrepancies between peripheral and central inflammatory markers, calling into question the potential validity of peripheral measures (Hannestad et al., 2013; Sandiego et al., 2015). Molecular imaging and post-mortem analyses provide direct measures of central cytokine levels and microglial activation, and this may be used to provide more accurate measures of neuroinflammatory signatures, as well as potentially validate findings from studies of peripheral measures concentrations of cytokine levels in ASD. In addition, a more nuanced understanding of the mediating (pro-) or suppressing (anti-) inflammatory responses of specific cytokines should be addressed. Although ASD is typically characterized as a pro-inflammatory condition (Haroon, Raison, & Miller, 2012), this categorization is not wholly consistent within the literature (Krakowiak et al., 2015; Molloy et al., 2006), and may, therefore, be too simplistic given the multiple functions of specific cytokines (Cavaillon, 2001).

Neuroinflammatory profiles in ASD provide a promising opportunity to better understand the heterogeneous presentations and biological mechanisms of heterogeneous reward-oriented behaviors in individuals with ASD. Researchers have begun to evaluate the potential of inflammatory markers, particularly cytokines, to serve as viable biomarkers of treatment response to ASD pharmacological interventions (for review see Masi et al., 2017), but more research is still needed to understand the how these immune signatures might characterize individual behavioral presentations, and, in turn, guide diagnostic decisions and treatment planning in ASD (Colburn et al., 2001). Although there are strong theoretical linkages between neuroinflammation and impaired reward processing in ASD, to date no research has empirically examined this association. Future research will be needed to directly assess the influence of neuroinflammation on reward-oriented behaviors and neural processes in individuals with ASD. More broadly, it will be vital to understand what

differentiates neuroimmunological disruptions that result in ASD from those that predispose to other psychiatric disorders, which have also been linked to immune dysregulation (e.g., schizophrenia, major depression). Differentiating the role immunology plays in the etiology of different psychiatric disorders may provide insights into the behavioral impact of specific neuroinflammatory aberrations. To date, the literature suggests a complex interaction between maternal and fetal genotype and heightened immune responsivity determines risk for the development of ASD (Traglia et al., 2018). As previously mentioned, it is also possible that the timing, duration, and severity of the immunological insult may result in unique behavioral presentations. Because both timing and development appear crucial in accurately understanding the mechanisms by which these immunological disruptions take effect, future studies should continue to employ a developmental framework and examine the long-term impacts of acute and prolonged immune dysregulation.

An additional future line of research should address the effects of neuroinflammation and subsequent nigrostriatal dopamine dysregulation on motor systems in ASD, given the strong influence of neuroinflammation on motor systems (Felger & Treadway, 2017). Motor disturbances are present in many individuals with ASD, and these impairments represent some of the earliest indicators of dysfunction in the disorder (Fatemi et al., 2012; Gowen & Hamilton, 2013). Notably, much of the neuroinflammation literature in ASD points to significant inflammation-induced impairment in the cerebellum (Vargas et al., 2005), a brain region critically-involved in sensorimotor control and perception (Manto et al., 2012).

Clearly, neural systems mediated primarily by non-dopaminergic mechanisms influence neuroinflammation and ASD symptom expression. For example, one such candidate system is serotonergic (5-HT) pathways: 5-Hydroxytryptamine produces inflammation via the 5-HT2A receptor (Pierce, Xie, Peroutka, Green, & Levine, 1995), serotonin antagonists reduce the severity of acute inflammatory episodes (Harbuz et al., 1996), and serotonin depletion reduces inflammation (Harbuz, Marti, Lightman, & Jessop, 1998). It is noteworthy in this regard that modulation of the release of 5-HT from dorsal raphe neurons in the nucleus accumbens bidirectionally modifies sociability in a mouse model (16p11.2 deletion mice) of ASD (Walsh et al., 2018). Additionally, chronic administration of 5-HT agents increase dopamine D3 receptor gene expression in the shell of the nucleus accumbens (Lammers, Diaz, Schwartz, & Sokoloff, 2000a, 2000b) and nonclinical studies in humans have demonstrated that 5-HT acts as a modulator of positive affect (Zald & Depue, 2001). Although no studies to date have assessed the effects of 5-HT agents on neuroinflammatory and reward processes in ASD, molecular imaging studies have documented 5-HT abnormalities in ASD (Chandana et al., 2005; Chugani, 2002) and 5-HT agents have been shown to improve ASD symptoms in some (Williams, Wheeler, Silove, & Hazell, 2011) but not all (King et al., 2009) studies, suggesting that agents that impact 5-HT systems remain a promising avenue for future drug development in ASD (Veenstra-VanderWeele et al., 2012).

In summary, emerging evidence suggests dysregulation of the neuroimmune system in ASD may provide insight into the etiology, maintenance, and heterogeneity of the disorder across development. These heightened neuroinflammatory responses in ASD appear to preferentially impact corticostriatal, and particularly mesolimbic, dopamine functioning, and may, therefore, represent a mechanistic account of reward processing deficits in ASD. Future

research is needed to better understand the complexities of immune dysfunction in ASD and its relation to dopamine dysregulation, particularly over the course of development. Continued empirical investigations of these linkages will help researchers and clinicians better understand the heterogeneous presentation of reward processing impairments in ASD and may serve to improve diagnosis, treatment selection, and treatment response monitoring for individuals with the disorder.

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Highlights

- Brain inflammation has been observed in individuals with autism
- Brain inflammation impacts reward-related behaviors and dopamine functioning.
- This review suggests that brain inflammation impairs reward processing in autism.
- This linkage, suggests anti-inflammatory treatments should be investigated to treat autism.

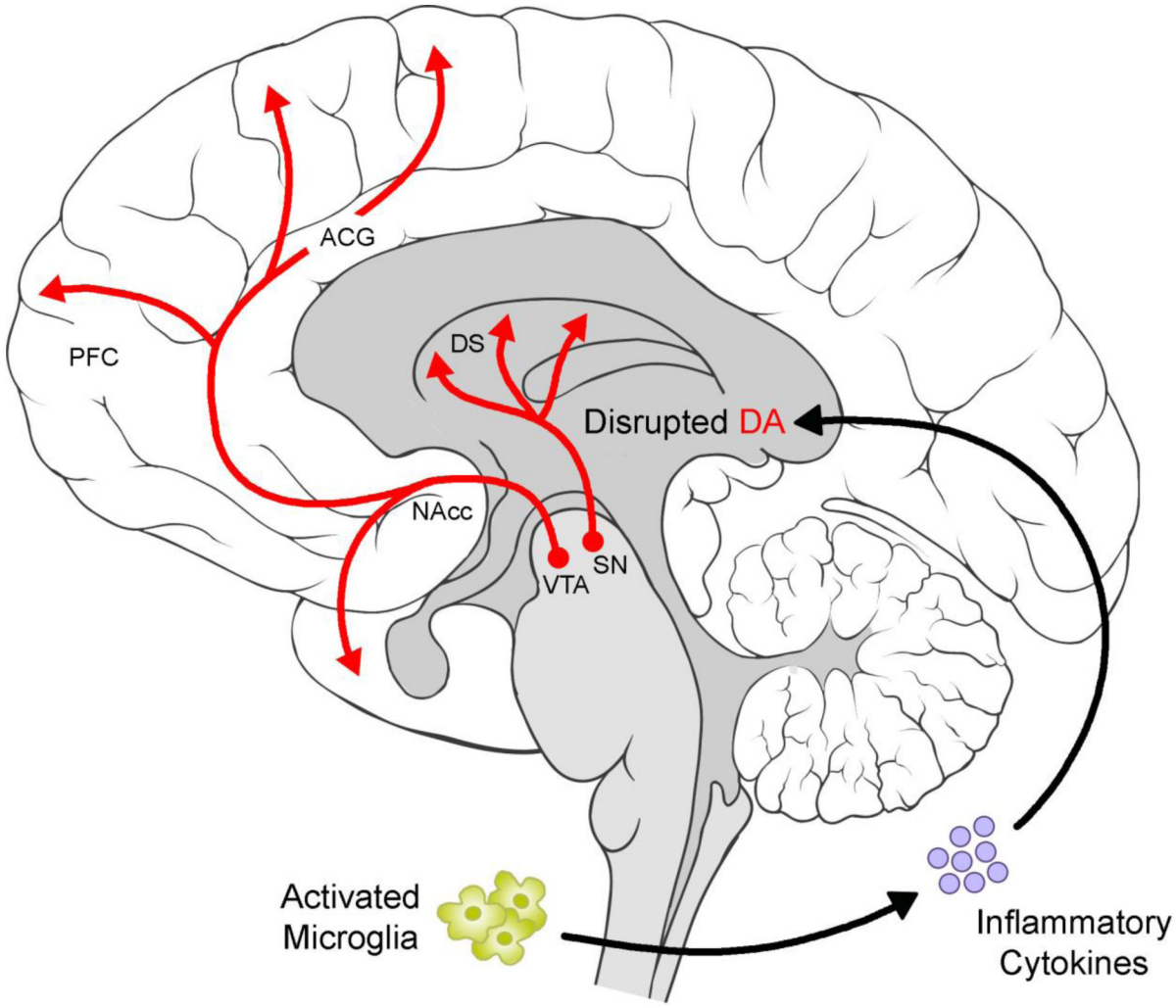

Figure 1.

Activated microglia produce inflammatory cytokines, which contribute to impaired dopaminergic functioning within midbrain and corticostriatal regions (for a review see Felger & Treadway, 2017). ACG = anterior cingulate gyrus, DA = dopamine, DS = dorsal striatum, NAcc = nucleus accumbens, PFC = prefrontal cortex, SN = substantia nigra, VTA = ventral tegmental area. Brain art adapted from illustrations created by Patrick Lynch, medical illustrator, and C. Carl Jaffe, MD, cardiologist (available at https://commons.wikimedia.org/wiki/File:Brain_human_lateral_view.svg and https://commons.wikimedia.org/wiki/File:Brain_human_sagittal_section.svg) and licensed under a Creative Commons Attribution 2.5 Generic License, 2006 (CC BY 2.5).

Table 1

Evidence of neuroinflammation-induced dopamine alterations within corticostriatal brain regions in rodent MIA models of ASD

Dopamine Marker	Developmental Stage	Sex	Region	Finding	Study
Prenatal LPS Exposure					
DA	Peripubertal	Male/Female	NAcc	↓	(Romero et al., 2010)
DA	Adult	Male/Female	NAcc	↑	(Romero et al., 2010)
DA	Adult	Male	Striatum	↓	(Kirsten, Taricano, Flório, et al., 2010)
DA	Adult	Female	Striatum	↓	(Soto et al., 2013)
DOPAC	Adult	Male	Striatum	↓	(Kirsten, Taricano, Flório, et al., 2010)
DOPAC	Adult	Female	Striatum	↓	(Soto et al., 2013)
HVA	Adult	Male	Striatum	↓	(Kirsten, Taricano, Flório, et al., 2010)
HVA	Adult	Male/Female	Hypothalamus	↓	(Kirsten & Bernardi, 2017)
HVA	Adult	Female	Striatum	↓	(Soto et al., 2013)
Prenatal Poly I:C Exposure					
D_1 Receptor Binding	Adult	Male/Female	DS, NAcc Shell	↑	(Vuillermot et al., 2010)
D_1 Receptor Binding	Adult	Male	PFC	↓	(Meyer, Nyffeler, et al., 2008)
D_2 Receptor Binding	Adult	Male	PFC	↓	(Meyer, Nyffeler, et al., 2008)
D_2 Receptor Binding	Adult	Male/Female	Striatum	↓	(Ozawa et al., 2006)
DA	Adult	Male/Female	Striatum	↑	(Zuckerman, Rehavi, Nachman, & Weiner, 2003)
DA	Fetal and Adult	Male/Female	SN	↑	(Vuillermot et al., 2010)
DA	Adult	Male/Female	VTA	↑	(Vuillermot et al., 2010)
DAT	Peripubertal	Male/Female	DS, NAcc Core, NAcc Shell	↓	(Vuillermot et al., 2010)
DAT	Peripubertal	Male/Female	NAcc	↓	(Vuillermot et al., 2010)
DAT	Fetal	Male/Female	VTA, SN	↑	(Meyer, Engler, Weber, Schedlowski, & Feldon, 2008)
DOPAC	Adult	Male/Female	Striatum	↑	(Ozawa et al., 2006)
TH	Adult	Male	DS	↑	(Meyer, Nyffeler, et al., 2008)
TH	Fetal	Male/Female	DS	↑	(Vuillermot et al., 2010)
TH	Peripubertal	Male/Female	DS, NAcc Core, NAcc Shell	↓	(Vuillermot et al., 2010)
TH	Adult	Male/Female	NAcc Core, NAcc Shell	↑	(Vuillermot et al., 2010)
TH	Fetal	Male/Female	VTA, SN	↑	(Meyer, Engler, et al., 2008)

Note. DA = dopamine; MIA = maternal immune activation; ASD = autism spectrum disorder; DAT = dopamine transporter; DOPAC = dihydroxyphenylacetic acid; HVA = homovanillic acid; TH = tyrosine hydroxylase; cerebral cortex; DS = dorsal striatum; NAcc = nucleus accumbens; PFC = prefrontal cortex; SN = substantia nigra; VTA = ventral tegmental area

Table 2

Studies demonstrating Corticostriatal Neuroinflammation in ASD

Neuroinflammatory Marker	Sample	Technique	Region	Study
Microglial Activation	ASD, TDC Adults	PET Imaging	ACG, MFG, OFC	(Suzuki et al., 2013)
Anti-brain Antibody Reactivity	ASD, TDC Children	Western Immunoblotting	CN, CX	(Singh & Rivas, 2004)
Anti-brain Antibody Reactivity	ASD, TDC Children	Western Immunoblotting	CN, PT, PFC, CG	(Singer et al., 2006)
Anti-brain Antibody Reactivity	ASD, TDC Children	ELISA	PT	(Singer et al., 2006)
Astroglial Activation	ASD, TDC Post-mortem	Western Immunoblotting	ACG, MFG	(Vargas et al., 2005)
Cytokine: TGF-β1	ASD, TDC Post-mortem	Protein Tissue Arrays	ACG, MFG	(Vargas et al., 2005)
Cytokine: TNF-α	ASD, TDC Post-mortem	Multiplexed Bead Analysis	CX	(Li et al., 2009)
Cytokine: IFN-γ	ASD, TDC Post-mortem	Multiplexed Bead Analysis	CX	(Li et al., 2009)
Cytokine: IL-6	ASD, TDC Post-mortem	Protein Tissue Arrays	ACG	(Vargas et al., 2005)
Cytokine: IL-6	ASD, TDC Post-mortem	Multiplexed Bead Analysis	CX	(Li et al., 2009)
Cytokine: IL-10	ASD, TDC Post-mortem	Protein Tissue Arrays	ACG	(Vargas et al., 2005)
Microglial Activation	ASD, TDC Post-mortem	Iba-1	PFC	(Morgan et al., 2010)
Microglial Density	ASD, TDC Post-mortem	Iba-1	PFC	(Morgan et al., 2010)
Microglial Density	ASD, TDC Post-mortem	Immunocytochemistry	FI	(Tetreault et al., 2012)
Microglia-Neuron Clustering	ASD, TDC Post-mortem	K-function Spatial Clustering	PFC	(Morgan et al., 2012)

Note. ASD = autism spectrum disorder; TDC = typically developing control; ELISA = enzyme-linked immunosorbent assay; Iba-1 = Iba-1 Immunohistochemistry Protocol; ACG = anterior cingulate gyrus; CG = cingulate gyrus; CN = caudate nucleus; CX = cerebral cortex; FI = frontoinsular cortex; MFG = medial frontal gyrus; OFC = orbitofrontal cortex; PFC = prefrontal cortex; PT = putamen