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Title: Prenatal exposure to environmental insults and enhanced risk of developing *Schizophrenia and Autism Spectrum Disorder*: focus on biological pathways and epigenetic mechanisms

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ABSTRACT

When considering neurodevelopmental disorders (NDDs), Schizophrenia (SZ) and Autism Spectrum Disorder (ASD) are considered to be among the most severe in term of prevalence, morbidity and impact on the society.

Similar features and overlapping symptoms have been observed at multiple levels, suggesting common pathophysiological bases. Indeed, recent genome-wide association studies (GWAS) and epidemiological data report shared vulnerability genes and environmental triggers across the two disorders. In this review, we will discuss the possible biological mechanisms, including glutamatergic and GABAergic neurotransmissions, inflammatory signals and oxidative stress related systems, which are targeted by adverse environmental exposures and that have been associated with the future development of *SZ and ASD*. We will also discuss the emerging role of the gut microbiome as possible interplay between environment, immune system and brain development. Finally, we will describe the involvement of epigenetic mechanisms in the maintenance of long-lasting effects of adverse environments early in life. This will allow us to better understand the pathophysiology of these NDDs, and also to identify novel targets for future treatment strategies.

Key words: schizophrenia; autism; neurodevelopmental disorders; brain development; prenatal stress; prenatal infections; microbiota; biological systems; inflammation; epigenetics; DNA methylation

Content

1. INTRODUCTION

Neurodevelopmental disorders (NDDs) represent a group of diseases characterized by an altered development of the Central Nervous System (CNS) that leads to the manifestation of brain dysfunctions later in life and that may be associated with neuropsychiatric problems or impaired motor function, learning, language or non-verbal communication. Due to their chronicity and their severity, NDDs impose tremendous burdens on the affected individuals, and, in turn, on their families and society in general (Silberberg et al., 2015).

NDDs comprise a broad spectrum of disorders, including Gilles de la Tourette syndrome, Intellectual Disability (ID), cortical dysplasia-focal epilepsy syndrome, Autism Spectrum Disorder (ASD), Attention Deficit Hyperactivity Disorder (ADHD), Pitt-Hopkins syndrome, and Schizophrenia (SZ) (Poot, 2015). *Among the different NDDs, SZ and ASD are considered to be among the most severe disorders in terms of prevalence, morbidity and impact to the society, as discussed in the following paragraphs (Castillejos et al., 2018; Kirkbride et al., 2012; Lyall et al., 2017; Silberberg et al., 2015).*

SZ is a severe psychiatric disorder that leads to great disability and distress. It has a lifetime prevalence of ~1% and according to the World Health Organization it has been labeled as one of the top ten causes of disability in developed countries worldwide (Murray and Lopez, 2017). Family, twin and adoption studies have demonstrated a high heritability, proving the involvement of genetic factors in this disorder (Mattheisen et al., 2012; Tang et al., 2017). The disease onset is typically during late adolescence or early adulthood and it is characterized by the presence of positive, negative and/or cognitive symptoms (Meyer et al., 2011; Miyamoto et al., 2012). Positive symptoms refer to psychopathological features that include delusions, disordered thinking, disorganized speech and visual/auditory hallucinations; negative symptoms refer to social impairment, lack of motivation, poverty of speech, affective blunting and inattention (Lee et al., 2012; Tandon et al., 2013); finally, cognitive symptoms include disturbances in executive functions and working memory (Meyer et al., 2011).

ASD is characterized by impairments in social interaction and communication and by the presence of repetitive behaviors (Bhati, 2013; Fakhoury, 2015; Hansen et al., 2015; Rapin and Tuchman, 2008). Overt symptoms of ASD often begin by the age of 6 months, they become established within the 2nd or 3rd year of age and tend to persist throughout life (Rapin and Tuchman, 2008). In other cases, children may show no

recognizable signs of ASD but then they may begin detaching socially and losing previously acquired language and social skills between 1 and 3 years of age. ASD symptoms may be different in affected children, but some of the most common symptoms include: i) difficulty in interpreting social cues, such as body language, facial expressions and tone of voice, ii) difficulty in empathizing and understanding other people's perspectives, iii) repetitive behaviors or interests, iv) difficulty in regulating emotions, and v) deficits in verbal communication and in understanding language.

Importantly, the reported prevalence of ASD has widely increased during the past 3 decades, ranging from 1% to 2.6% in the last years. This apparent increase in ASD prevalence can be attributed to several reasons, including changes in reporting practices, greater public awareness and/or an earlier diagnosis (Hansen et al., 2015; Kogan et al., 2009).

Years ago ASD was considered an early manifestation of SZ (often referred to as "childhood psychosis"), and about one-third of SZ childhood onset cases received first a diagnosis of ASD (Rapoport et al., 2009). Although SZ is mainly manifested during adulthood, whereas ASD during childhood, the two disorders share vulnerability genes and mechanisms (Autism Spectrum Disorders Working Group of The Psychiatric Genomics, 2017; Waltereit et al., 2014), as suggested by recent findings from epidemiological and genome-wide association studies (GWAS). Moreover, similar clinical features, including deficits in social interaction and cognition, disruption of emotional processing and sensorimotor gating, and impairments in executive functions can be observed at multiple levels in both SZ and ASD (Biotteau et al., 2016; Cheung et al., 2010; Keller et al., 2017; Meyer and Feldon, 2009; Toal et al., 2009). *For example, social withdrawal, communication impairment, and poor eye contact seen in ASD children are similar to the negative symptoms observed in adolescents with SZ. In a recent paper, Zhang and collaborators (Zhang et al., 2015) have shown that patients with ASD and SZ have similar impairments in decision-making under ambiguity and under risk. Moreover, ASD subjects have been shown to be more sensitive to the magnitude of loss than to the frequency of loss, whereas SZ patients displayed more sensitivity to the frequency of loss than to the magnitude of loss. According to the authors, this last finding suggests that the impaired performance in ASD subjects might be due to the deficits in the feedback processing, whereas in SZ patients it might be due to the deficits in executive functions (Zhang et al., 2015).*

When trying to understand the pathogenic mechanisms associated with these two disorders, several gaps still need to be filled. *According to the "neurodevelopmental hypothesis", SZ and ASD may be the consequence of exposures to adverse external or internal insults during critical periods of brain development (Chohan et al., 2014; Panaccione et al., 2013), highlighting the prenatal and early postnatal environment as critical players of these diseases*. Indeed, it is well known that brain development requires an accurate coordination and timing of many contributing molecular systems and several environmental insults occurring during this period may alter this process with immediate or delayed consequences on brain function (Lewis and Levitt, 2002). Importantly, depending on the timing of the insult, common disruptions could have transient or marked effects leading to chronic disability (Horvath and Mirnics, 2015; Insel and Wang, 2010; Lewis and Levitt, 2002). The temporal correlation between the onset of several NDDs and the period of synapse assembly has led to the hypothesis that deficits in synaptic maturation, connectivity or stabilization represent a core neuropathological mechanism underlying NDDs. Indeed, the appearance of early NDDs symptoms often coincides with the period of massive synaptogenesis in the developing brain that occurs during the first 2 years of an infant's growth. Importantly, the notion that many NDDs can be considered "synaptopathies" is also strongly supported by the preponderance of penetrant mutations in genes associated with synaptic structure and function (Zoghbi and Bear, 2012), including those that are located at the pre or post-synaptic compartments.

In addition to the environmental insults, also the individual genetic background plays a critical role: indeed, the same insult can exert different effects in different subjects, depending on the disease-predisposing genetic variants on their genome (Horvath and Mirnics, 2015). However, NDDs are complex disorders, thus we need to keep in mind that single genes are not able, when taken alone, to determine the basis for the development of the illness. Rather, it is a network of "vulnerability genes" that interact with each other and with adverse environmental factors in increasing the susceptibility of developing NDDs. In support of this, recent GWAS have shown a polygenic component, which comprises multiple "susceptibility" genes, underlying the risk of SZ and ASD (Tang et al., 2017). These common risk variants have been implicated in molecular abnormalities pertaining to neurotransmitter receptors, enzymes, protein kinases, and transcription and translation processes (Harrison and Weinberger, 2005; Oddi et al., 2013; Won et al., 2014), which result in a

disturbed ability of information processing within several brain circuits responsible for the symptoms of the disorders.

On these bases, the main purpose of this review is to focus the attention on the main biological systems implicated in the pathogenesis of SZ and ASD, highlighting how common pre and postnatal environmental insults, genetic background and their interaction during brain development could modulate the risk of developing these disorders. Since SZ and ASD share common molecular mechanisms, in this review, we will describe the complex interplay between different biological systems in the development of such disorders and we will highlight similarities as well as differences in their pathological mechanisms.

2. EARLY-LIFE ENVIRONMENTAL INSULTS AND NDDs

Epidemiological and experimental findings indicate that early life adversities occurring during the pre, peri and postnatal period can act as detrimental factors that increase the vulnerability of developing NDDs (Lyall et al., 2014b; Ryan and Saffery, 2014). Different environmental factors including exposure to maternal stress, psychiatric disorders, alcohol, drugs, chemicals, poor nutrition and infections during pregnancy have a negative impact on the brain development during fetal life and have been found associated with the future development of SZ and ASD (Fakhoury, 2015; Gardener et al., 2009; Heyer and Meredith, 2017; Wallace, 2016; Wong et al., 2015) (see Figure 1). *Specifically, human epidemiological and mechanistic findings, together with preclinical studies conducted in animals, suggest that the most powerful early life adversities that can shape the offspring's development and health later in life are maternal stress and maternal immune activation (Van den Bergh et al., 2017).* During the last years, a particular interest has been focused on the mechanisms by which these environmental insults can lead to behavioral alterations in the offspring, as these, if properly targeted, may prevent the future development of these disorders. *Given the extensive body of novel findings associated with prenatal stress and prenatal infections, we have focused on these two factors when discussing the negative effects of exposures to early-life environmental factors on mental health.*

All these findings will be described in details in the following paragraphs.

2.1. Prenatal stress

Prenatal stress is described as a physiological, maternal adverse experience which can influence the offspring's neurodevelopment in multiple ways (Gumusoglu et al., 2017). Stressful events during embryogenesis are indeed hypothesized to have deleterious consequences on fetal brain development, which may contribute to the manifestation of psychiatric symptoms as well as several other chronic diseases later in life (Boksa, 2010). During the last years, several studies conducted both in human and animal models have investigated the consequences of prenatal exposure to stress focusing on the association between maternal stress and neurodevelopmental features in the offspring.

Human studies

As extensively discussed in an excellent review (Van den Bergh et al., 2017), prenatal exposure to maternal stress may affect the newborn's cognitive development, affectivity, and temperament (Van den Bergh et al., 2017). Interestingly, by analyzing longitudinal prospective studies, the authors reported the presence of negative outcomes in the offspring's mental health (including in this domain: anxiety, depression, SZ, ASD and bipolar disorder, among others) following a variety of maternal stressors, such as maternal psychological stress, (i.e. general or pregnancy-specific anxiety and depressive symptoms), major stressful life events experienced by the mother (i.e. illnesses or deaths in the close family, financial and relationship problems, house moves and car accident) or exposures to a natural disaster (Van den Bergh et al., 2017). Against this background, several studies have sought to identify the molecular and biological underpinnings of such association and most of the results suggested that stressful life events during pregnancy could cause an increase in the maternal concentrations of stress-related hormones, such as cortisol and placental corticotropin-releasing hormone (CRH), which in turn may influence fetal brain development and growth (Charil et al., 2010; Davis and Sandman, 2010; de Weerth et al., 2013; Werner et al., 2013). However, against these positive findings, other studies found only moderate correlations between prenatal stress and maternal cortisol levels (Bleker et al., 2017; Diego et al., 2006; Wadhwa et al., 1996), suggesting that maternal cortisol during pregnancy is mainly affected by biological and lifestyle factors, including gestational age, maternal age, time of day, parity, pre-pregnancy body mass index (BMI), CRP levels, fetal sex, smoking behavior, self-reported sleep sufficiency and employment. Thus, it is clear that additional

studies are warranted to further investigate and clarify this relationship, and the assumption that maternal stress during pregnancy results in increased cortisol levels should be interpreted with caution.

Importantly, both the duration and the timing of maternal stress exposure may play a critical role leading to consequences with a different impact. For example, in the context of SZ, Fineberg and colleagues have recently observed that daily stress during the beginning of the second trimester of pregnancy is associated with increased risk of SZ in male offspring in adulthood (Fineberg et al., 2016). However, contrasting results have been reported regarding the timing of maternal stress, in the context of SZ. Indeed, several population-based studies have indicated that severe maternal stress in the first trimester of pregnancy is associated with an increased risk of SZ in the offspring (Khashan et al., 2008; Malaspina et al., 2008). On the other hand, Scheinost and colleagues have provided preliminary human data demonstrating an increasing connectivity in limbic system structures across the third trimester of gestation (Scheinost et al., 2017). These findings pinpoint the third trimester of pregnancy as the most critical period for the alterations in specific neural networks, also observed in SZ subjects (Scheinost et al., 2017).

Similarly, a recent study has indicated maternal stress/depressive mood in pregnancy as common risk factors for ASD and ADHD (Say et al., 2016). The effects of maternal bereavement stress on the offspring's psychopathology have been investigated at different time points, such as pre-conception, prenatal and postnatal periods, and, interestingly, a different effect on behavior according to the temporal window when stress occurred has been observed: exposure to stress over the third-trimester has been associated with an increased risk for both ASD and ADHD, whereas bereavement stress during the second postnatal year was associated with an increased risk to develop ASD only (Class et al., 2014).

Animal studies

Different paradigms of prenatal stress have been employed in rodents and they mainly relied on a variable, unpredictable stress regimen (consisting of restraint stress, forced swim stress, overcrowding, exposure to bright light and food deprivation), or on one single stressor (e.g. severe restraint stress or inescapable foot shock), applied for one or two weeks to pregnant dams before delivery (Lussier and Stevens, 2016; Richetto and Riva, 2014; Stevens et al., 2013). Several lines of evidence indicate that there are several long-lasting consequences of prenatal stress exposure, which include alterations both at behavioral and molecular level.

For example, prenatal stress has been associated with the development of inhibited behaviors in the offspring, such as reduced activity in an open field, reduced social preference, and increased anxiety-like behavior in the elevated plus maze and light–dark box (Grigoryan and Segal, 2013; Laloux et al., 2012; Marrocco et al., 2012). Moreover, independently from the type of the stressor applied, all these studies have consistently shown that prolonged prenatal manipulations impair spatial learning and memory, with an effect that can be observed not only in adolescence but also in adulthood (Fumagalli et al., 2007; Giovanoli et al., 2013; Luoni et al., 2017; Richetto and Riva, 2014). It is important to note that in the majority of the above reported studies, animals have been exposed to stressful insults over the last week of gestation; thus, an exposure to stress during different temporal windows may have different effects on neurodevelopment, supporting the notion that alterations in brain formation also depends on the intensity, the duration, and the time of exposure (Weinstock, 2008).

Overall, these data suggest that prenatal stress is linked to abnormal cognitive, behavioral and psychosocial outcomes in human cohorts as well as in animal models, and increases the risk of developing SZ and ASD. *Thus, pregnant women and their offspring should be recognized as a vulnerable population and protected from stressful and adverse conditions. Moreover, the extent to which the offspring are affected depends also on the postnatal and adult environment (Monaghan and Haussmann, 2015), suggesting that increased awareness and support could be instrumental in protecting at-risk individuals.*

2.2. Prenatal infections

The possible contribution of infections to the development of SZ and ASD during the first period of life has recently aroused a great deal of interest, as prenatal infections are known to induce pathophysiological changes in the fetal environment, negatively affecting the normal course of brain development in the offspring and thus determining long-lasting consequences in postnatal life (Flinkkila et al., 2016; Meyer, 2013).

Human studies

During the last years, extensive epidemiological data demonstrate that exposure to bacterial, viral (including rubella, measles, polio and herpes simplex) or protozoan parasite (e.g. Toxoplasma gondii) infections during fetal life increases the risk of developing SZ and ASD (Babulas et al., 2006; Brown, 2012; Brown et al., 2004; Brown and Derkits, 2010; Brown et al., 2014; Currenti, 2010; Khandaker et al., 2013; Mortensen et al., 2007; Shi et al., 2003; Sorensen et al., 2009; Spann et al., 2017). Importantly, the varied nature of the different immunogenic molecules supports the notion that the association between exposure to prenatal infections and SZ or ASD is not pathogen-specific, but could actually be driven by factors that are common to all infections, such as elevated levels of pro-inflammatory cytokines.

Cytokines are small secreted proteins that control the nature, duration, and intensity of the immune response and that are generated in response to infections (Goines and Ashwood, 2013). They are highly pleiotropic, and can act in an autocrine, paracrine, and/or endocrine fashion. Cytokines are mainly produced by immune cells, including dendritic cells, macrophages, neutrophils, T and B cells, though many additional cell types, including neurons, produce and respond to them (Ramesh et al., 2013). In addition, cytokines have important effects on the fetal brain development because they are involved in directing important neurodevelopmental trajectories, including temporal regulation of neurogenesis and gliogenesis, progenitor migration, proliferation and axon path-finding, neuronal survival and synapse modulation and elimination (Boulanger, 2009; Deverman and Patterson, 2009; Goines and Ashwood, 2013; Suvisaari and Mantere, 2013). The physiological trajectory of fetal brain development thus requires a specific balance of constitutively expressed cytokines in the maternal and fetal environment. This balance is normally tightly controlled, but, in case of maternal immune response to infections, the excessively produced maternal cytokines cross the placental boundary (Estes and McAllister, 2016a), invade the fetal compartments (Reisinger et al., 2015; Zaretsky et al., 2004) and stimulate the *de novo* synthesis of cytokines in the fetal brain (Ashdown et al., 2006) (see Figure 1).

Ultimately, this cytokine imbalance can compromise the functional and structural integrity of the developing brain with short and long-lasting consequences, and this has been suggested to be a shared pathological mechanism underlying both SZ and ASD (Abdallah et al., 2013; Bilbo and Schwarz, 2012; Knuesel et al., 2014; Patterson, 2009). *Indeed, it has been demonstrated that elevated levels of fetal pro-inflammatory cytokines (i.e. Interleukin (IL)-6, IL-1β, and Tumor Necrosis Factor (TNF)-α) in response to maternal*

infections can produce pathological changes in brain morphology that are similar to those observed in subjects affected by SZ or ASD (Heyer and Meredith, 2017).

Animal studies

Human epidemiological data are mainly supported by studies in animal models, where the effects of infections during pregnancy or in the early postnatal period can be investigated with a cause-consequence approach.

Fatemi and colleagues were the first to develop an experimental mouse model of prenatal exposure to the human influenza virus, demonstrating that immunological insults during the early phases of pregnancy are associated with deficits in social interaction, pre-pulse inhibition and exploratory behavior in the adult offspring (Fatemi et al., 2004; Honda-Okubo et al., 2014; Jurgens et al., 2012; Shi et al., 2003; Xia et al., 2014). To date, the most widely used animal model of prenatal infection, also called maternal immune activation (MIA), is based on the administration of immunogenic substances, such as lipopolysaccharide (LPS) or polyriboinosinic–polyribocytidilic acid (polyI:C). LPS is an inherent cell wall component of gram-negative bacteria, which is recognized mainly by the pathogen recognition receptor transmembrane protein toll-like receptor (TLR) 4, whereas polyI:C is a synthetic analog of double-stranded RNA that efficiently stimulates an immune response via TLR3 activation (Meyer, 2014). The administration of both LPS or polyI:C to pregnant rodents acutely enhances the levels of pro-inflammatory cytokines in the mother's blood, placenta, amniotic fluid and fetus and can cause microglia activation and induction of the pro-inflammatory transcription factors in the fetal and neonatal brain (Meyer, 2014; Meyer et al., 2005; Saadani-Makki et al., 2008). Although their effect is mainly acute, the consequences of such exposures can persist over time, and some of them are still present in the adult offspring, including a vast array of behavioral, molecular and neurochemical abnormalities relevant to NDDs (Estes and McAllister, 2016b; Meyer, 2014), with an effect size that depends on the precise timing of infection.

Prenatally exposed offspring also recapitulate neuropathological differences relevant to SZ and ASD. For example, animal studies showed that rats exposed to prenatal polyI:C on gestation day (GD) 15 exhibit histopathological abnormalities and cell loss in the hippocampus (Zuckerman et al., 2003), as well as decreased hippocampal, prefrontal, cortical and striatal volume, and enlarged ventricles (Piontkewitz et al.,

2011), common hallmarks of SZ. On the other hand, adult mice exposed to prenatal infections have been shown to display reduced Purkinje neurons in the cerebellum (Naviaux et al., 2013; Shi et al., 2009), mirroring a common pathological feature that is observed also in ASD.

Importantly, many behavioral and neuropathological findings have been recently extended and confirmed also in non-human primates, which have a strong translational value due to their biological similarity to humans (Bauman et al., 2014; Machado et al., 2015; Weir et al., 2015).

One of the first cytokines that is increased in the serum of pregnant dams after MIA is IL-6, a pro-inflammatory cytokine that regulates self-renewal among neuronal precursor cells, directs neuronal migration and promotes cell survival and neurite outgrowth (Goines and Ashwood, 2013). Interestingly, an increase in IL-6 levels could be sufficient to alter brain development and behavior in the offspring (Estes and McAllister, 2016a), as demonstrated by studies in which the administration of single inflammatory cytokines (IL-6 or IL-2) is sufficient in precipitating the adult pathological phenotype (Ponzio et al., 2007; Smith et al., 2007). *For example, daily injections of IL-2 to pregnant mice during mid-gestation led to immunological changes and ASD-like behavioral abnormalities in the offspring (Ponzio et al., 2007). Moreover, significant levels of IL-2 were found in the amniotic fluid and tissues obtained from the same dams, confirming that IL-2, as well as other cytokines, can cross the placenta, directly reach the fetus and affect its development*.

From an opposite point of view, when LPS or/and polyI:C are co-administered with antibodies blocking IL-6 or IL-1β, the detrimental effects of prenatal infection on brain and behavioral pathology are prevented (Girard et al., 2010; Smith et al., 2007).

Moreover, recent evidence suggests that IL-17 may act downstream of IL-6 in mediating the effects of MIA (Choi et al., 2016). In detail, using several genetic mouse models, the authors demonstrated that IL-17, which is secreted by TH17 cells in the mother's circulating blood, crosses the placenta and acts in the offspring's brain. IL-17, once produced, promotes the cellular expression of IL-17 receptor that, in turn, further exacerbates the IL-17 signaling activation in the fetal brain (Choi et al., 2016).

These studies highlight, once more, how specific pro-inflammatory cytokines, which are commonly produced in a variety of infections, could be critical in mediating the detrimental effects of prenatal exposure to MIA.

How can these pro-inflammatory stimuli translate the dysfunctions that we observe in patients with NDDs? To date, it is still unclear how pro-inflammatory cytokines alter brain development. Indeed, while maternal immune activation triggers inflammation within the mother, the altered cytokine profiles that have been measured in the fetal brain do not necessarily recapitulate a classic inflammatory response (Estes and McAllister, 2015). Thus, how these changes in cytokines levels could increase the risk of developing NDDs remains a critical question to be addressed. One possibility is that prenatal infections could lead to long-lasting changes in the expression of immune molecules such as those related to the major histocompatibility complex I (MHCI), known to regulate neural connectivity and function in the offspring (Coiro et al., 2015; Estes and McAllister, 2015).

Moreover, epigenetic mechanisms have been suggested to be involved in the maintenance of long-term effects of prenatal adversities and also in the maintenance of the dysfunctions (Basil et al., 2014; Hollins et al., 2014; Labouesse et al., 2015; Richetto et al., 2017). However, how and if these epigenetic modifications are induced by alterations in fetal brain cytokine levels remains unknown. Interestingly, epigenetic mechanisms may also explain the transgenerational transmission of the vulnerability in developing these NDDs. Indeed, Weber-Stadlbauer and colleagues have shown that prenatal immune activation can shape the disease risk also in future descendants, as it has been found to negatively affect brain functions and behavior also in multiple generations. In particular, it seems that some behavioral features such as reduced sociability and increased cued fear expression can be observed until the third-generation offspring of immune-challenged ancestors, supporting a transgenerational non-genetic inheritance of pathological traits following *in-utero* immune activation (Weber-Stadlbauer et al., 2017).

3. BIOLOGICAL SYSTEMS INVOLVED IN NDDs

Prenatal exposures to different insults induce alterations in several biological systems leading to an increased vulnerability of developing SZ and ASD later in life; moreover, as different insults lead to alterations in common biological systems, this could also explain why some of the symptoms are shared across NDDs.

Several biological systems have been proposed to play a pivotal role, including: i) neurotransmitter systems (Chiocchetti et al., 2014; Coyle, 2012; Deidda et al., 2014; Fatemi and Folsom, 2014; Kantrowitz and Javitt,

2012; Karam et al., 2010; Rojas, 2014; Steiner et al., 2013), ii) inflammation (McDougle et al., 2015; Meyer, 2013; Potvin et al., 2008; Saetre et al., 2007; van Berckel et al., 2008), and iii) redox signaling (Clay et al., 2011; Do et al., 2009; Gysin et al., 2011; Porokhovnik et al., 2015). A deregulation in all these pathways and their reciprocal interactions have been proposed to represent one "central hub" underlying the development and the onset of both SZ and ASD (Steullet et al., 2017; Steullet et al., 2016).

In addition, a growing number of studies has recently proposed the gut microbiota (GMB) as a key player mediating the effect of environmental factors on our immune system and brain functioning, adding further complexity to the pathogenetic mechanisms associated with NDDs. Disturbances in the GMB composition have been, indeed, found both in patients with SZ and ASD, suggesting that its alterations may influence the activation of the peripheral and central immune and inflammatory system leading to alterations in brain functions (Dinan and Cryan, 2017; Hsiao et al., 2013; Khodaie-Ardakani et al., 2014; Pyndt Jorgensen et al., 2015). How the GMB is linked to the immune system, neurotransmitters and redox signaling is recently being investigated by various groups, and will definitely be the focus of future research in the field.

In this section, we will thus describe the different biological systems involved in SZ and ASD, highlighting possible similarities or differences in their pathological mechanisms.

3.1 Alterations in neurotransmitter systems

During brain development, neurotransmitters not only enable synaptic communication between cells but they also fulfill additional roles in CNS morphogenesis and neuronal proliferation, migration and differentiation (Heyer and Meredith, 2017). Therefore, any environmental insults that interfere with neurotransmission can potentially produce acute and/or long-lasting alterations in CNS structure and function, contributing to understand the mechanisms underlying NDDs. Below we will describe the main known alterations associated with neurotransmission in the context of SZ and ASD.

3.1.1 Glutamatergic system

Glutamate plays an important role in brain development, neuronal migration, differentiation, cell survival and synaptogenesis (Zheng et al., 2016). Glutamatergic receptors are divided into two broad families, the ionotropic and metabotropic subtypes; ionotropic receptors are differentiated based upon sensitivity to the

synthetic glutamate derivatives N-methyl-D-aspartate (NMDA), α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and kainate (Balasuriya et al., 2013). Metabotropic receptors are G protein-coupled receptors that usually mediate long-term neuromodulatory effects of glutamate and are divided into different groups based on the coupling effector and ligand sensitivity (Kantrowitz and Javitt, 2012). NMDA receptors (NMDARs) are composed of a heteromeric assembly of subunits where, at least one subunit, as the Glutamate Ionotropic Receptor NMDA Type Subunit 1 (NR1), combines with NR2 and/or rarely NR3 subunits. To increase the complexity, there are eight different splicing variants of the gene encoding for the NR1 subunit and six other variants that encode for different forms of the NR2 (NR2A, NR2B, NR2C, and NR2D) and NR3 (NR3A and NR3B) subunits, leading to a multitude of different NMDARs variants (Geddes et al., 2011).

An accurate expression and regulation of NMDARs in the brain is pivotal for learning and memory processes as well as for cortical plasticity and maturation, especially during the "critical brain developmental temporal window" (Kahn and Sommer, 2015). Accumulating evidence has indicated that the maturation of brain circuitry, during the early stages of neurodevelopment, corresponds to a switch in the NMDARs subunits (i.e. NR2B to NR2A, and NR3A to NR3B), which contributes to the transition from juvenile to "adult" neural processing (Dumas, 2005; Henson et al., 2010; Lum et al., 2016). For example, the NR2B subunit is highly expressed prenatally and its levels decrease after birth in most of the brain regions, suggesting a potential role in cellular migration and differentiation, as well as in synaptic plasticity-related mechanisms. Mutation-related disruptions within this subunit have been, indeed, linked to a number of neurodevelopmental phenotypes characterized by alterations in circuit formation, neuronal connectivity, synaptic plasticity, and excitatory transmission (Hu et al., 2016). A deregulation in NMDARs subunits has been observed in post-mortem tissues obtained from SZ patients (Geddes et al., 2011; Kristiansen et al., 2007; Weickert et al., 2013) and, also, in the brains of SZ animal models (see Table 1) (Gunduz-Bruce, 2009; Lisman et al., 2008; Tarabeux et al., 2011).

Several studies have suggested that a hypo-function in NMDARs within the limbic system during neurodevelopment could contribute to alterations in brain development and to psychopathology later in life. This hypothesis was postulated following the observation that NMDARs antagonists (such as phencyclidine (PCP), dizocilpine (MK-801) and ketamine) caused SZ-like symptoms in control subjects (Frohlich and Van

Horn, 2014) and in animal models (Feng et al., 2010; McNally et al., 2013; Purkayastha et al., 2015). Similar abnormalities in glutamatergic signaling occur in ASD, as indicated by studies conducted in the brains obtained from ASD patients (Blatt et al., 2001; Fedder and Sabo, 2015; Purcell et al., 2001) and in several animal models of ASD (Sceniak et al., 2016) (Table 1). However, in the last years, contrasting results about the role of glutamate in the pathogenesis of ASD have been reported. For example, according to the glutamate "hypo-function hypothesis", animal models of hypoglutamatergia have been described as showing ASD-related behavioral phenotypes, such as defective habituation, restricted behavioral repertoire and inability to change behavioral paradigm (Choudhury et al., 2012; Nilsson et al., 2004). However, an increase in glutamate concentration has been identified in the blood of ASD patients as compared to healthy subjects (see Table 1) (Aldred et al., 2003; Cai et al., 2016; Shinohe et al., 2006; Zheng et al., 2016), suggesting a "glutamate hyper-function theory" (Rojas, 2014). In this context, Aldred and collaborators supported the latter theory as, by measuring plasma amino acid levels in ASD patients, their siblings, and parents and comparing them versus control groups, they reported increased levels of glutamic acid, phenylalanine, asparagine, tyrosine, alanine, and lysine in all ASD patients as compared to controls. Only glutamine plasma levels were reduced, whereas other amino acids were at normal levels. As also discussed by the authors, these findings suggest that the presence of an increased glutamate metabolism, possibly genetically driven, is associated with ASD in children (Aldred et al., 2003). These data have been replicated in independent studies, where again higher levels of glutamate have been reported in the serum of ASD patients as compared with controls (Shinohe et al., 2006). Moreover, a recent meta-analysis (Zheng et al., 2016) has confirmed the presence of higher glutamate levels in ASD subjects, although only in plasma samples, suggesting the potential role of blood glutamate levels as potential peripheral biomarkers for ASD.

Interestingly, early life adversities (such as stress and infections) during the prenatal period can also negatively affect the glutamatergic pathway, suggesting that this neurotransmitter system could be a convergence target for different insults acting during fetal development. In particular, several studies have observed altered expression of glutamatergic receptors (Fatemi et al., 2017; Meyer et al., 2008; Pascual et al., 2017; Rahman et al., 2017; Wischhof et al., 2015), aberrant glutamatergic transmission (Marrocco et al., 2012) and plasticity (Cavalier et al., 2018) in adult animals exposed to prenatal stress or prenatal infections.

3.1.2 GABAergic system

Another neurotransmitter that has been implicated in the pathogenesis of NDDs is γ-aminobutyric acid (GABA). Indeed, glutamatergic neurons interact with GABAergic interneurons (Lewis et al., 2005), especially basket and chandelier cells, that strongly regulate and coordinate the output from cortical pyramidal neurons (Fish et al., 2013). These cells limit an excessive pyramidal glutamatergic activity by exerting a powerful feedback inhibitory action (Snyder and Gao, 2013), and an impairment of GABAergic interneurons has been associated with a striking disinhibition of the pyramidal glutamatergic efferent activity and, as a consequence, with an elevated and uncoordinated activation throughout the corticolimbic circuit, resulting in cognitive impairments.

The main findings in supporting this alteration come from post-mortem brain and neuroimaging studies which have identified the presence of abnormalities in GABA neurotransmission in association with poor cognitive functioning (Karam et al., 2010; Purkayastha et al., 2015), including the presence of alterations in GABAergic interneuron density or distribution in several brain areas of both SZ and ASD post-mortem brain tissues (Chance et al., 2005; Di Rosa et al., 2009; Joshi et al., 2012; Konradi et al., 2011; Morris et al., 2008; Wang and Kriegstein, 2011) (Table 2).

GABA is the major inhibitory neurotransmitter in the brain and its synthesis, at cortical level, is controlled by the enzyme glutamic acid decarboxylase 67 kD isoform (GAD67), whose levels have been found reduced in post-mortem tissues obtained from both SZ and ASD patients as compared to controls (Curley et al., 2011; Davis et al., 2016; Fatemi et al., 2004; Harvey and Boksa, 2012). Although less investigated, the expression levels of other GABA-related enzymes, such as the presynaptic GABA membrane transporter (GAT1), responsible for the reuptake of extracellular GABA, and the vesicular GABA transporter (vGAT), which loads GABA into presynaptic vesicles, have been also found to be reduced in the prefrontal cortex (PFC) of both patients (Fung et al., 2011; Hoftman et al., 2015; Lewis et al., 2012; Yu et al., 2013) as well as in animal models of SZ and ASD (Richetto et al., 2014; Sgado et al., 2013) (Table 2).

Importantly, a deficiency in these genes alters neuronal GABA content leading to alterations in synaptic physiology. The main effects seem to occur in a particular subset of cortical GABA neurons, mainly in parvalbumin-containing interneurons (PV+), which are fast-spiking, non adapting GABAergic neurons

(basket or chandelier cells) interconnected via gap junctions (Fukuda et al., 2006) that form inhibitory synapses with pyramidal neurons (Bartos et al., 2007; Steullet et al., 2016). The maturation of PV+ and their associated extracellular matrix occurs mainly during postnatal development of cortical network plasticity (Morishita and Hensch, 2008). Moreover, it has been shown that PV+, especially the basket cells, contribute *to learning, memory consolidation and retrieval* (Donato et al., 2013) and promote neuronal progeny survival and development in the hippocampus (Song et al., 2013a). *Importantly, especially in PFC, PV+ undergo a complete maturation during adolescence (O'Donnell, 2012), rendering them highly sensitive to environmental insults that act early in life. Indeed, as extensively discussed by Steullet and colleagues, many studies demonstrate that environmental insults during this period, such as stress or infections, can affect the maturation trajectory of PV+, leading to impaired high frequency neuronal synchrony (Uhlhaas and Singer, 2010), and thus contributing to the sensory, social and cognitive symptoms found in patients with SZ and ASD (Steullet et al., 2017). Maternal stress, for example, has been repeatedly shown to affect GABAergic interneuron development. Specifically, several studies have observed alterations in the migration of GABAergic progenitors following restraint stress starting on embryonic day (E) 12 (Stevens et al., 2013), and disturbances in proliferation of neurons destined to be PV+ interneurons following repeated restraint stress from E15 to E17 (Uchida et al., 2014). Interestingly, Lussier and colleagues, who also implemented a maternal stress paradigm of restraint stress (45 minutes a day, starting on E12), observed a delay in the maturation of GABAergic population from juvenile to adult development that was associated with reduced social preference and increased anxiety (Lussier and Stevens, 2016). These results could be consistent with the notion that cerebellar GABAergic projection neurons and interneurons are generated according to distinct strategies (Leto and Rossi, 2012). Moreover, the generation of the variety of interneurons appears to be largely dependent on extrinsic influences, so that their types and numbers can be adjusted in response to specific demands that may arise during the course of cerebellar development, including acute or chronic stress (Leto et al., 2012).*

The presence of a delay in GABAergic development after birth up to adolescence due to prenatal stress has been also observed, in a similar way, as a consequence of exposures to maternal infections during pregnancy (Richetto et al., 2014).

3.1.3 Excitatory/Inhibitory balance

When we talk about neuronal excitability we refer to the balance between excitatory (E) and inhibitory (I) neurotransmission (Takesian and Hensch, 2013). It is well known that a well-maintained E/I balance is essential to normal cortical function, whereas an excessive shift towards excitation could lead to a wide range of deficits in perception, cognition, memory, and motor function (Froemke, 2015). It has been suggested that differences in the balance between the brain's excitatory glutamate and inhibitory GABA systems may represent another common feature across the different NDDs (Agarwal et al., 2014; Ajram et al., 2017; Krystal et al., 2017). *For example, it has been hypothesized that, in SZ, a hypofunction of NMDARs, due to NMDA loss or dysfunction primarily on cortical interneurons, can lead to a reduction in network inhibition that, in turn, can determine a secondary overstimulation of the glutamatergic system and a shift in the E/I balance towards excitation (Kehrer et al., 2008; Meunier et al., 2017). This shift, in turn, is thought to result in alterations in the synchronous oscillations of network activity, which are essential for timed transmission of information in cortical regions (Gonzalez-Burgos et al., 2015). Specifically, oscillatory activity at gamma (~30–80 Hz) frequency bands is crucial for cognition (Fries, 2009; Wang, 2010), and abnormalities in this synchronized activity have been suggested to play a central role in the pathophysiology of SZ (Gonzalez-Burgos et al., 2015; Uhlhaas and Singer, 2010).*

Ajram and colleagues compared the E/I balance and functional connectivity of the PFC in adult men with and without ASD by implementing proton magnetic resonance spectroscopy ([1H] MRS) and resting-state functional magnetic resonance imaging (fMRI) (Ajram et al., 2017). Interestingly, they found that the responsivity of the E/I system and the associated functional networks in ASD men was regulated differently from controls. Indeed, although no baseline differences in the levels of cortical glutamate or GABA were found between ASD patients and controls, riluzole, *a drug that inhibits the release of glutamic acid*, increased a PFC inhibitory index in ASD men but decreased it in controls. Riluzole also increased prefrontal functional connectivity, which was absent at baseline in ASD, to control levels. These findings suggest that E/I balance can be shifted in adults thanks to a pharmacological treatment and that responsivity is significantly different in ASD patients versus controls.

Overall, these data suggest the complementary role of neurotransmitters in the modulation of excitatory and inhibitory synapses and highlight how alterations in one neurotransmitter system can have consequences on the regulation of synaptic efficacy and plasticity by other neurotransmitters.

3.2 Inflammatory-related processes

As we have discussed previously, alterations in the immune and inflammatory related systems during brain development exert severe consequences for brain functioning later in life. Several studies have tried to investigate the presence of a chronic inflammatory state, especially in the brain, in patients with SZ and ASD, leading to controversial results, especially in SZ (Khandaker et al., 2015). Indeed, while higher levels of inflammation have been reported and well replicated in ASD, with consistent findings both in the periphery and in the CNS (Masi et al., 2015; Meyer et al., 2011), the evidence of persistent inflammation in SZ is still controversial, probably also due to the difficulty of dissecting, in these patients, the effects of treatment from those more specifically related to the chronicity of the illness (Trepanier et al., 2016). Below we report the main findings coming from recent reviews/meta-analyses.

3.2.1 Peripheral levels of cytokines and chemokines

Alterations in the levels of cytokines and chemokines, well known mediators of the cross-talk between the CNS and the immune system (Potvin et al., 2008), have been described in peripheral blood of both SZ and ASD (Lv et al., 2015) and have been also related with specific symptoms (Table 3).

According to the recent review performed by Prata and collaborators, pro-inflammatory cytokines are increased in the blood of SZ and ASD patients, but, so far, there is not a *validated panel of pro-inflammatory molecules* that can provide a reliable inflammatory signature for these disorders (Prata et al., 2017).

Regarding SZ, two meta-analyses clearly illustrated that IL-6 was consistently elevated in serum and plasma of SZ patients (Miller et al., 2011; Potvin et al., 2008), whereas IL-1β and TNF-α were found to be increased only in one meta-analysis (Miller et al., 2011) but not in the other (Potvin et al., 2008).

More recently, the expression levels of five cytokines (IL-1β, IL-2 IL-6, IL-8 and IL-18) were measured in the peripheral blood of controls and of SZ patients. The protein levels of eight cytokines (IL-1β, IL-2, IL-6, IL-8, IL-10, IL-12, IFNγ and TNFα) were also measured in serum and plasma obtained from the same

cohorts. A decrease in the anti-inflammatory IL-2 mRNA and an increase in serum IL-6, IL-8 and TNF-α protein levels were found in SZ subjects compared to controls (Boerrigter et al., 2017). Therefore, a greater percentage of SZ patients (about 48%) was grouped into the elevated inflammatory biotype compared to controls (33%), confirming that SZ subjects are more likely to have elevated levels of inflammation compared to controls. Blood cytokine protein levels did not correlate with mRNA levels; however, plasma levels of only two cytokines allowed to distinguish controls from SZ patients, with significantly increased levels of IL-1β in the control group and of IL-8 in the SZ group. Similarly, in another study (Noto et al., 2015), the diagnosis of SZ was accompanied by a specific cytokine-chemokine profile, such as increased levels of CCL11, CCL3, soluble TNF receptors 1 and 2 (sTNF-R1 and sTNF-R2), and decreased levels of CXCL10, TNF-α, IL-2, and IL-4. Using five of these inflammatory markers (sTNF-R1 and sTNF-R2, CCL11, CXCL10, IL-4), the authors found a sensitivity of 70% and a specificity of 89.4% for the diagnosis of SZ, *suggesting that some inflammatory molecules may be used as reliable biomarkers for the diagnosis of SZ and treatment resistance*.

In line with the previously mentioned studies, other reviews and meta-analyses of the literature have also shown that increased blood levels of IL-1β, IL-6 and TNF-α are consistently reported in patients at the early onset of SZ (Di Nicola et al., 2013; Miller et al., 2011; Mondelli et al., 2011).

Interestingly, the levels of some of these inflammatory molecules have been also associated with SZ symptoms. For example, IL-2, soluble IL-2 receptor (sIL-2R), IL-6 and IL1-RA have been positively linked with negative symptoms and duration of illness (Asevedo et al., 2014; Hope et al., 2013; Kim et al., 2000) and, TNF-α serum levels were positively associated with severe psychopathological symptoms (Lv et al., 2015). In addition, TNF-α levels have been associated with dysfunction of thought, perception, and behavior and plasma sTNF-R1 levels were also significantly correlated with positive symptoms of SZ (Hope et al., 2013). To this regard, Misiak and collaborators performed a systematic review of studies investigating the association between peripheral blood levels of cytokines and C-reactive protein (CRP) and cognition in SZ patients (Misiak et al., 2017). Most consistent results indicated worse cognitive performance in SZ patients with higher CRP levels. Less consistent evidence suggested better cognitive functioning of SZ patients with higher levels of TNF-α. Evidence for the involvement of other cytokines in cognitive impairment in SZ was less convincing due to discordant results or scarcity of studies.

Although longitudinal studies of inflammatory markers and subsequent psychotic disorders are scarce, findings from the Avon Longitudinal Study of Parents and Children (ALSPAC) birth cohort suggested that increased serum levels of the pro-inflammatory cytokine IL-6 at age 9 was associated with 2-fold increased risk of developing a psychotic disorder at age 18 (Khandaker et al., 2015). *Another prospective study reported that an increased risk of late SZ onset was also associated with increased serum CRP concentrations measured, on average, 7-8 years before hospitalization with SZ and SZ-like psychosis (Wium-Andersen et al., 2014).*

Antipsychotic-naive first-episode psychosis and acute psychotic relapse have been also associated with increased serum concentrations of IL-6 and other pro-inflammatory cytokines, such as TNFα, IL-1β, INFγ, and decreased serum concentrations of anti-inflammatory cytokine IL-10, which are normalised after remission of symptoms due to antipsychotic treatment (Miller et al., 2011).

In the context of ASD, several studies have investigated the levels of a number of cytokines in peripheral blood samples and cerebrospinal fluid (CSF) of ASD children (Madore et al., 2016) (Table 3).

For example, increased serum levels of Monocyte Chemotactic Protein-1 (MCP-1) and decreased levels of Regulated upon Activation Normal T-Cell Expressed and Secreted (RANTES) have been also associated with ASD across different samples including blood and CSF and reviewed by Zerbo and colleagues (Zerbo et al., 2014). All these observations have been also confirmed in the meta-analysis performed by Masi and collaborators on studies comparing plasma and serum concentrations of cytokines in unmedicated subjects with ASD and controls (Masi et al., 2015). The results show that the concentrations of IL-1β, IL-6, IL-8, INFγ, eotaxin and Monocyte Chemotactic Protein-1 (MCP-1) were significantly higher in the ASD subjects as compared with the control group, whereas concentrations of TGF-β1 were significantly lower.

3.2.2 Immune cell populations

Increasing evidence of altered immune function in SZ and ASD is also related to differences in populations of immune cells and in serum levels of antibodies (Bjorklund et al., 2016; Miller et al., 2013; Modabbernia et al., 2017; Prata et al., 2017) (Table 3).

A recent meta-analysis performed in drug-naïve SZ patients (Miller et al., 2013) has reported an increased number of total lymphocytes, including T lymphocytes (CD3+), T helper cells (CD4+), and a higher ratio

between T helper and T cytotoxic cells (CD4+/CD8+). In acutely relapsed patients, the authors also found a higher proportion of CD4+ and CD56+ cells (T helper and natural killer (NK) cells, respectively). After treatment, the CD4+/CD8+ ratio decreased, while the concentration of CD56+ cells increased.

Anomalies in T, B, NK and peripheral mononucleate cell function were also reported in ASD, as reviewed in Bjorklund et al. (Bjorklund et al., 2016). A reduced percentage of CD4+ T helper cells, lower number of T cells (CD2+) and lower percentages and number of total lymphocytes were identified in ASD subjects compared to controls (Ashwood et al., 2011b; Lopez-Cacho et al., 2016). From an immunological point of view, CD4+ T helper cell activities are fundamentally divided into T helper 1 (Th1) (cell-mediated immunity), and Th2 (humoral immunity) subsets. Th1 is the first-line of defense system primarily against viral, fungi, and protozoa, while Th2 helps the B-cells to produce antibodies (Hirahara and Nakayama, 2016). Many studies have indicated that ASD patients in comparison to controls have a diminished Th2 anti-inflammatory response and an increased Th1 pro-inflammatory cytokine response, as increased levels of IFNγ and IL-1RA, resulting in a Th1 skewing (Bjorklund et al., 2016; Croonenberghs et al., 2002; Goines et al., 2011).

Children diagnosed with ASD were reported to either have a reduced number of B-cells and an increased amount of NK cells in comparison to controls (Bressler et al., 2012), although recent findings seem to contradict this opinion (Heuer et al., 2012). This evidence may suggest that the reduction in immunoglobulin levels observed in ASD may be a consequence of B-cell depletion or impairment. Indeed, ASD children showed significantly reduced levels of plasma immunoglobulin (Ig)G and IgM compared to children with other developmental delays and controls (Heuer et al., 2008). This reduction correlated with behavioral severity and patients with the most reduced levels of IgG and IgM scored highest in behavioral tests. Moreover, in ASD, particularly in children with regressive ASD, a shift in the immunoglobulin composition in serum, with low-normal IgA and CD23-expressing B-cells, was observed (Wasilewska et al., 2012).

Several studies have also shown that macrophage and NK cell activities are altered in ASD. For example, several ligands of CCR4, such as CCL22 and CCL17, were reported to be elevated (Al-Ayadhi and Mostafa, 2013), and NK cells were approximately 40% higher in children diagnosed with ASD compared to controls. These data are in agreement with Enstrom and colleagues, who reported greater numbers of NK cells and increased gene expression of NK cell-related receptors and effector molecules in ASD children in

comparison to controls (Enstrom et al., 2010). According to the authors, abnormalities in NK cells in ASD may predispose individuals to the development of autoimmunity and/or adverse neuroimmune interactions during critical periods of development (Enstrom et al., 2010). Indeed, the presence of autoantibodies towards CNS proteins is a common finding in ASD and may reflect an ongoing inflammatory and/or an autoimmune process in individuals with ASD that could be started by abnormal NK cell activation (Ashwood et al., 2006).

3.2.3 Microglia activation

In the CNS, microglia and astrocytes are the most important immunological cells that regulate both the induction and limitation of inflammatory processes through the synthesis of pro- and anti-inflammatory cytokines and of various cell surface receptors, such as those crucial for antigen presentation (Perry and O'Connor, 2010; Ransohoff and Perry, 2009).

Microglia are the resident immune cells in the brain, which act in the context of injury and disease, whereas astrocytes are the largest glial cell population in the brain. Both microglia and astrocytes are capable of producing pro- and anti-inflammatory cytokines and, therefore, are considered immunocompetent cells (Paolicelli and Ferretti, 2017). In the presence of external insults, microglia are rapidly recruited to the site of damage where they phagocytose debris as well as dying cells. Historically segregated into 'resting' (or quiescent) and 'activated', it is now appreciated that microglia are never-resting cells that possess multifaceted and highly dynamic phenotypes, ranging from surveillant, proliferating, pruning, neuromodulatory, phagocytotic and inflammatory phenotypes (Gomez-Nicola and Perry, 2015). Given their multifaceted nature, it is thought that they can have, in different circumstances, either a neuroprotective or a neurotoxic role and, therefore, they may be the result, but also a further cause of neuronal damage (van Berckel et al., 2008). Removal of microglia during development, through both pharmacological and genetic methods, has been found able to exert a long and negative lasting impact on synaptic maturation and brain circuit formation (Nelson and Lenz, 2017). *In the context of NDDs, it is possible that severe perturbations of microglia activity, especially during the "critical" early neurodevelopmental periods, might drastically compromise the correct maturation and wiring of the brain. Further studies are warranted in order to confirm this hypothesis.*

An activation of microglia and astrocytes as well as an increase of the release of microglia related markers, including cytokines, have been reported both in patients with SZ and ASD (Patterson, 2009) (Table 3).

The activation of microglia not only causes increased levels of cytokines and chemokines, but is also related to the production of inducible nitric oxide (NO)-synthase (i-NOS) (Takano, 2015), which can have a toxic effect in neurons. Several studies have pointed out that an increase in NO leads to a decrease in NK cell function, which seems to be altered in both SZ and ASD (Enstrom et al., 2009; Karpinski et al., 2016).

Over the last years, the role of microglia in SZ and ASD has been widely investigated by several studies both in humans and in animals.

Human post-mortem studies

Post-mortem and neuroimaging studies have suggested that activated microglia occur in the brain of both SZ and ASD patients (Rodriguez and Kern, 2011; Steiner et al., 2008; Suzuki et al., 2013; Takano, 2010; van Berckel et al., 2008) (Table 3).

To date, post-mortem studies in SZ have reported mixed findings, possibly in relation to some methodological issues; indeed, most post-mortem studies have been conducted on relatively small samples, included mainly elderly subjects in whom incidental lesions are common, and have used different methods for counting astrocytes and microglia (Schnieder and Dwork, 2011).

The first evidence of the activation of microglia was provided in 1999 by Bayer and colleagues (Bayer et al., 1999) who conducted immunohistochemical analysis on post-mortem PFC and hippocampus of 14 SZ patients and 13 controls. By using the human major histocompatibility complex (MHC) class II antigen human leukocyte antigen-antigen D related (HLA-DR), which is expressed by dendritic cells, B cells, and monocytes/macrophages, as a marker, the authors found HLA-DR positive microglia in 3 of the 14 patients, but no activation of microglia in controls.

Later studies that employed more quantitative analyses reported elevated densities of HLA-DR-immunoreactive microglia in the PFC, with similar findings in the anterior cingulate and temporal cortex, between SZ patients and controls (Radewicz et al., 2000; Wierzba-Bobrowicz et al., 2005). A much larger study of 37 middle-aged SZ subjects found a higher density of HLA-DR-immunoreactive microglia in the white matter of the PFC relative to unaffected comparison subjects (Fillman et al., 2013b). Similarly, Garey

and collaborators identified that the number of microglia in SZ patients was higher than in controls: 28% increase in the frontal area and 57% in the temporal area. The authors hypothesized that early insult or congenital errors might have led to the recruitment of microglia to the site of the injury (Garey, 2010), with these cells remaining resident through to adulthood. This hypothesis assumes that permanent damage is caused early in life and that the brain does not have enough plasticity to counteract the damage, which would persist after a prolonged period.

However, not all studies relating to microglia density have reported differences between SZ and controls. For example, a study of 16 middle-aged SZ subjects found no difference in HLA-DR immunoreactive microglia density in the PFC, anterior cingulate cortex, hippocampus or medio-dorsal nucleus of the thalamus in SZ relative to unaffected comparison subjects (Steiner et al., 2006). A follow-up study performed by the same authors found a similar lack of effect of diagnosis on microglial density, but suicide was associated with higher HLA-DR positive cells (Steiner et al., 2008). A previous study of 23 elderly, chronically ill SZ subjects reported no change in the density of microglia immunoreactive for CD68+, a lysosomal marker for phagocytosis, in multiple cortical regions (Arnold et al., 1998).

Many studies have also measured markers of neuroinflammation in post-mortem brain samples from SZ patients. In the review performed by Trepanier and colleagues (Trepanier et al., 2016), for example, the authors report ten studies that evaluated cytokine and chemokine expression levels in post-mortem brains of SZ patients. INF-γ, IL-1β, TNF-α and TNF-α receptor 1 mRNA and protein levels have been found increased in the PFC of SZ patients compared to unaffected controls (Dean et al., 2013; Harris et al., 2012). A microarray analysis found a decrease in IL-8 and IL-1α mRNA levels in the temporal cortex of SZ patients as compared with controls, although microarray results were not validated by qPCR (Schmitt et al., 2011). Another study also found a decrease in IL-8 mRNA levels in the middle frontal gyrus of SZ subjects, whereas IL-1β, TNF-α, IL-18 and IL-6 were not changed (Fillman et al., 2014). Two more microarray studies also found decreases in CCL3 expression levels in the prefrontal cortex (Nakatani et al., 2006) and IL-13RA mRNA levels reduced in the temporal lobe (Durrenberger et al., 2015) of SZ patients.

Post-mortem studies have confirmed the increase in microglia activation also in ASD (Morgan et al., 2010; Pardo et al., 2013), as well as reduced number of neurons in the fusiform gyrus (van Kooten et al., 2008), which is one of the cortical regions supporting face processing. A similar reduction in the number of neurons

has been reported in the amygdale (Schumann and Amaral, 2006). Altered microglial profile and increased levels of inflammatory cytokines such as IFN-γ, IL-1β, IL-6, TNF-α and chemokines CCL-2 were found in the post-mortem brain tissue of individuals diagnosed with ASD (Morgan et al., 2010). Also, post-mortem temporal cortex samples from ASD and general population controls were assessed for transcriptome differences and it was observed that samples from ASD individuals showed increases in expression of immune-related genes (Garbett et al., 2008).

Human "in vivo" studies

More recent studies quantifying microglia activation *in vivo* have reported increased microglia activation (Bloomfield et al., 2016; Doorduin et al., 2009; Suzuki et al., 2013; van Berckel et al., 2008) supporting the role of neuroinflammation in the pathophysiology of both SZ and ASD (Table 3). With the advent of non-invasive methods of studying brain function, such as functional magnetic resonance imaging (fMRI) and positron emission tomography (PET), valuable information can be obtained. For instance, PET can be used to identify activated microglia based on the ability of some markers to selectively bind to microglia, once they are activated, but not when microglial cells are in resting condition. In a study conducted by Suzuki and colleagues, for example, the application of PET using [11C]-(R)-PK11195) revealed substantial activation of microglia in adult patients with ASD (Suzuki et al., 2013). However, the regional distribution was not different between these subjects and controls. No difference between SZ patients and controls has been found when the new radiomarker [18F]-FEPPA and a high-resolution research tomography were employed, both in gray and white matter brain regions (Kenk et al., 2015). However, in a very recent study using a novel radio-ligand, [C-11]-PBR28 (Bloomfield et al., 2016), the activity of microglia in SZ patients was found to be higher in comparison with controls. This agrees with other findings obtained using PET in the hippocampus of SZ patients (Doorduin et al., 2009) and in total gray matter of the brain within the first 5 years of disease onset (van Berckel et al., 2008).

Despite the fact that numerous studies have now pointed out an involvement of activated microglia in the pathogenesis of both SZ and ASD, recent reports have highlighted how this hypothesis could be based on equivocal evidence (Notter and Meyer, 2017; Pasternak et al., 2016; Trepanier et al., 2016). Specifically, a recent study by Notter and colleagues (Notter et al., 2017) challenges the validity of one of the most widely

used *in vivo* techniques for the assessment of inflammatory abnormalities along the clinical course of SZ, namely PET using radiolabeled ligands selective for the 18-kDa translocator protein (TSPO). Their translational approach, comprising of human SZ patients and an infection-mediated neurodevelopmental mouse model, failed to support the general assumption that low-grade central inflammation is mirrored by increased TSPO expression, thus suggesting that existing findings on microglial activation in SZ should be interpreted with caution.

Given the multifaceted nature of microglia, new experimental tools and analytical approaches are needed to meet the requirements of the functional diversity and dynamics of microglia, which could then shed light on the precise involvement of these cells in the pathophysiology of NDDs.

Animal model studies

In recent years, an increased interest has been focused on the role of microglia in early adverse event conditions. Indeed, different animal models of pre and perinatal stress/inflammation have been shown to induce both acute and long-lasting effects on microglia activity.

Regarding stressful events, it has been observed that prenatally stressed mice displayed higher numbers of ramified microglia in several brain regions analyzed at postnatal day (PND)1, with microglia morphology returning to normal by PND10 (Gomez-Nicola and Perry, 2015). Similar findings were reported in rats, with primary cultures of microglia isolated *from prenatally stressed animals* showing increased release of pro-inflammatory cytokines, including IL-1β, IL-18, TNF-a and IL-6, and reduction of IGF-1 (Slusarczyk et al., 2015). More subtle effects have been observed in animal models of early post-natal stress. Maternal deprivation during the first 2 weeks of life, for example, was associated with acute effects on hippocampal microglia, including larger soma size, increased release of IL-1β (Roque et al., 2016) and increased microglial surface area (Delpech et al., 2016). Delpech and collaborators (Delpech et al., 2016), however, reported that alterations in microglial morphology were transient and parameters normalized later at PND28. Long-lasting effects of early life stress were also reported in other brain areas. For example, increased microglia motility was observed in the sensorimotor cortex of adult mice that had experienced maternal deprivation (Takatsuru et al., 2015).

In the context of inflammation, several studies observed alterations in microglial density, morphology, phagocytotic activity, and gene and protein expression as a consequence of MIA (Esslinger et al., 2016; Manitz et al., 2016; Mattei et al., 2014; Mattei et al., 2017; Pratt et al., 2013; Ribeiro et al., 2013; Van den Eynde et al., 2014; Zhu et al., 2014a). However, in contrast, other authors did not observe any short- (Smolders et al., 2015), or long-lasting (Giovanoli et al., 2015; Giovanoli et al., 2016) changes in microglial density or in inflammatory markers expression following prenatal exposure to polyI:C. These inconsistencies might be due to the specific parameters implemented to assess microglial abnormalities, and call for further efforts in elucidating the effects of prenatal immune challenge on microglial functionality. Of note, recent studies observed that prenatal infection-induced microglial alterations are associated with various behavioral abnormalities. For example, Mattei and colleagues reported that maternal immune activation (MIA) leads to drastic changes in the transcriptome and phagocytic activity of microglial cells in the hippocampus of adult male offspring that is associated with SZ-like behavioral abnormalities. Interestingly, these cellular and behavioral deficits were reversed by minocycline antibiotic treatment (Mattei et al., 2017). These findings are consistent with a recent study that uncovers more pronounced differences in microglial distribution, arborization, cellular stress, and synaptic interactions in the hippocampus of male vs. female offspring exposed to polyI:C, with an effect that is accompanied by behavioral impairments, again observed in male animals only (Hui et al., 2018).

Recently, Gumusoglu and colleagues (Gumusoglu et al., 2017) have investigated the role of IL-6 in embryonic and adult microglia of prenatally stressed mice. The authors have reported that both prenatal stress and IL-6 exposure contributed to an increased density of multivacuolated microglia in the embryonic cortical plate at earlier stages of development, suggesting either a specific period of susceptibility or the influence of stress duration for these effects. This was prevented by IL-6 blockade during prenatal stress. As with embryonic microglia, prenatal IL-6 recapitulated prenatal stress-induced changes in adult microglia. Furthermore, prenatal IL-6 was able to recapitulate the delay in GABAergic progenitor migration caused by prenatal stress.

These findings suggest that microglia can play a crucial role in mediating vulnerability to stress and infections. However, the molecular mechanisms by which microglia mediate synaptic and behavioral changes in early-stress and infection models are far from been understood.

3.2.4 Effects of early environmental factors on the immune/inflammatory system

Recent lines of evidence have suggested that exposure to early life inflammation renders the individual more vulnerable to a "second adverse hit" represented, for example, by other external insults, suggesting that latent immune-related vulnerability does not become manifest until an additional adverse exposure ("the second hit"), stress- or inflammation-related, occurs (Debost et al., 2017; Feigenson et al., 2014; Plant et al., 2016). For example, combined exposure to prenatal immune challenge and peri-pubertal stress has been shown to induce synergistic pathological effects on adult behavioral functions in animals (Giovanoli et al., 2013) and increase the risk of SZ in humans (Debost et al., 2017). Interestingly, this 'priming' effect has been observed also with respect to exposure to early life adversities. Indeed, *recent studies have also suggested that exposures to childhood trauma may promote enduring liability for psychosis, including SZ, whereas more recent adverse events may act as precipitants. A longitudinal 10-year prospective cohort study of 3 021 adolescents and young adults showed that experiences of childhood trauma and recent life events are strongly correlated and interacted additively in increasing the risk for psychosis (Lataster et al., 2012). These findings support that early life stress may render individuals more vulnerable to later adversities increasing the risk of developing NDDs, including SZ.*

Fellerhoff and collaborators have described a very striking example of the uniqueness of the individual response to inflammation/infections (Fellerhoff and Wank, 2011). The authors investigated serious pneumonia in two children, who later developed ASD and SZ, respectively. Since both children presented very high antibody titers against the pathogen Chlamydophila, the authors investigated whether the DNA of these bacteria was present in brain samples of another cohort of SZ patients. Interestingly, the bacterial DNA was found to be four times higher in these patients than in controls. According to these findings, a subsequent study (Prata et al., 2017) has suggested that the molecular profile of the brains of SZ patients may not be significantly different from those observed in ASD individuals. The difference may reside on how the brain reacts to stressful events and, in particular, on how the innate immune system responds to these challenges. In this context, the later onset of SZ might be related to some immunomodulatory abilities of the brain to keep inflammation in a dormant state.

Aside of the recognized role of prenatal exposure to infections in the pathogenesis of NDDs, more detailed studies are needed to better understand the role and the effects of both inflammation and immune system responses in SZ and ASD. Indeed, given the common contribution of prenatal immune activation to the pathogenesis of both SZ and ASD, it is feasible to postulate that differences in immune system response during postnatal periods could influence the trajectory versus these two NDDs.

3.3 Dysbiosis of gut microbiota

The human gut microbiota (GMB) refers to the community of microorganisms, including bacteria, archaea, viruses and some unicellular eukaryotes that live in the gastrointestinal tract (D'Argenio and Salvatore, 2015). Among all the species, Firmicutes (species such as *Lactobacillus*, *Clostridium*, *Enterococcus*) and Bacteroidetes (species such as *Bacteroides*) represent the most abundant phyla found in the human gut (Qin et al., 2010). During the first days of life, the GMB is unstable and of low diversity, shifting its composition over the first few years to resemble an adult-like profile by the age of 3 (Kelly et al., 2016). Also, the birth delivery mode seems to influence the GMB composition (Clarke et al., 2014): vaginally delivered infants are colonized by the fecal and vaginal bacteria of the mother, most notably *Lactobacilli*, whereas infants delivered by Caesarean section are colonized by other bacteria from the skin of the mother and from environmental sources (Dinan and Cryan, 2017; Kelly et al., 2016). Other factors such as gestational age, breast-feeding mode and antibiotic use can also influence the trajectory of GMB composition.

In recent years, the understanding of the GMB's influence on brain functions has increasingly grown, and mounting evidence indicates that microbiota have an important role in modulating both physiological and pathological behavioral processes. Indeed, the GMB produces a wide range of bioactive compounds, such as short chain fatty acids, conjugated linoleic acid and neurotransmitters (Barrett et al., 2012; O'Mahony et al., 2015), which could influence CNS functions both via systemic circulation and via indirect actions on afferent neuronal routes such as the vagus nerve (Cryan and Dinan, 2012; Dinan and Cryan, 2015).

Human studies

The GMB has recently emerged as a key player in mediating the association between environmental insults in pre and/or postnatal life and the future development of SZ and ASD (Borre et al., 2014; Madore et al.,

2016). For example, experimental studies have revealed alterations in the GMB composition, often referred to as dysbiosis, in patients with NDDs as compared to healthy controls (Parracho et al., 2005; Rosenfeld, 2015). *In a recent study, Schwarz and colleagues (Schwarz et al., 2018) investigated the GMB composition in SZ and related psychotic disorders. They observed that patients with first-episode psychosis exhibited an altered taxonomic signature compared to non-psychiatric subjects, with a relatively increased abundance of the families Lactobacillaceae, Halothiobacillaceae, Brucellaceae, and Micrococcineae, and decreased Veillonellaceae. Particularly, Lactobacillaceae were overrepresented among the taxa that were more abundant in SZ patients.*

In addition, antipsychotics, such as olanzapine, have been shown able to affect the GMB composition (Bahr et al., 2015; Davey et al., 2013; Morgan et al., 2014), and an antibiotic treatment was also able to potentiate the effect of antipsychotics in patients with SZ (Khodaie-Ardakani et al., 2014).

Several studies investigating the faecal GMB in ASD patients have also been conducted, although with contrasting results. Indeed, in the Tomova's study, a significant decrease in the *Bacteroidetes/Firmicutes* ratio and an increase in the abundance of *Lactobacillus spp*. and *Desulfovibrio spp*. were found in the stool of ASD children as compared to controls. Moreover, administration of probiotics normalized the Bacteroidetes/Firmicutes ratio and the Desulfovibrio spp. levels, and this effect correlated with a reduction of the intestinal inflammation in ASD children (Tomova et al., 2015). Conversely, in a recent study, no significant difference in GMB diversity or composition was detected between ASD children and their non-affected siblings; however, this lack of effect could be due to the small sample size used in this study (Son et al., 2015).

In this context, several lines of evidence have shown that stress exposures in different periods of life can also reshape the GMB composition (Kelly et al., 2017). Indeed, infants of mothers with a history of high self-reported stress and high salivary cortisol concentrations during pregnancy had significantly higher relative abundances of Proteobacteria known to contain pathogens (related to Escherichia, Serratia, and Enterobacter), and lower relative abundances of Lactobacilli and Bifidobacteria, altogether characteristics of a potentially increased level of inflammation (Zijlmans et al., 2015).

Animal studies

Initial evidence for the hypothesis that GMB composition could be linked to alterations in the CNS stemmed from germ-free (GF) mouse models, in which the commensal gastro-intestinal (GI) microbiota is missing throughout early brain development and maturation. *In a pioneering study, Sudo and colleagues demonstrated that GF mice display functional changes in the hypothalamus-pituitary-adrenal (HPA) axis (Sudo et al., 2004). In their study, GF mice exposed to mild stress displayed elevated adrenocorticotropic hormone and corticosterone release compared to control mice with normal gut microflora; interestingly, this stress response was fully reversed by reconstitution with Bifidobacterium infantis and partially reversed by colonization with fecal matter from control mice (Sudo et al., 2004).* This observation was followed by subsequent independent studies that implicated changes in the GMB composition in anxiety behavior (Bercik et al., 2011; Clarke et al., 2014; Neufeld et al., 2011), cognitive processes (Gareau et al., 2011), exploratory behavior (Bercik et al., 2011), social behavior (Desbonnet et al., 2014), and behavioral responses to drugs of abuse (Kiraly et al., 2016). Interestingly, behavioral alterations in GF mice can be ameliorated by the administration of *Lactobacilli* and *Bifidobacteria* or by the transplantation of microbiota from control animals (Neufeld et al., 2011).

When considering the effects of prenatal stress on GMB, a pioneering study by Bailey and Coe established that early life maternal separation resulted in a significant decrease in fecal Lactobacillus abundance on day 3 post-separation, which was correlated with stress-related behaviors in the exposed rhesus monkeys (Bailey and Coe, 1999). Studies that are more recent uncovered similar findings in rodents. Indeed, in a mouse model of social disruption, stress altered the GMB profile and increased the levels of the pro-inflammatory cytokine IL-6 (Bailey et al., 2011). Moreover, in rats, late gestational stress induced increased HPA-axis reactivity in response to stress, cognitive impairments and altered GMB composition, suggesting that prenatal stress also affects the GMB with implications for physiological outcomes in the offspring (Golubeva et al., 2015). In addition, in a mouse model of prenatal stress, maternal stress decreased the abundance of vaginal Lactobacillus, resulting in decreased transmission of this bacterium to offspring, which paralleled changes in metabolites involved in energy balance, and with disruptions of amino acid profiles in the developing brain (Jasarevic et al., 2015).

Interestingly, it has also been reported that the GMB composition is altered in animal models for SZ. Indeed, Pyndt Jorgensen and collaborators found that a sub-chronic phencyclidine (PCP) treatment in rats, known to

induce a SZ-like behavior in rodents, altered the GMB composition; moreover, they showed that such changes highly correlated with a worse memory performance; conversely, further supporting the role of gut bacteria in the development of this behavior, administration of the antibiotic ampicillin abolished the effects of PCP-induced memory deficit (Pyndt Jorgensen et al., 2015).

The effects of prenatal infection on GMB have also been addressed. For example, Hsiao and collaborators (Hsiao et al., 2013) demonstrated that MIA-induced microbial shifts in certain gut microbial communities were associated with subsequent onset of behavioral and gastrointestinal changes that resemble some of the ASD symptoms. Indeed, alongside microbial dysbiosis, the authors observed defects in intestinal permeability, elevated inflammatory cytokines and behavioral alterations following MIA. Importantly, treatment with the commensal bacterium Bacteroides fragilis reversed most of the physiological, neurological, metabolic, and immunological abnormalities. Findings from this study thus highlight that a 'leaky gut' and related elevations in pro-inflammatory cytokines are involved in intestinal dysbiosis and suggest that re-equilibration of commensal bacteria may improve gastrointestinal and behavioral abnormalities observed in ASD.

Similarly, MIA offspring displayed decreased intestinal barrier integrity and an altered GMB (Hsiao et al., 2013). In particular, taxonomic changes within the Clostridia and Bacteroidia classes accounted for most of the dysbiosis observed in the fecal samples of these offspring. An enrichment in Lachnospiraceae, Porphyromonadaceae, Prevotellaceae, unclassified Bacteriodales, while an enrichment in Ruminococcaceae, Erysipelotrichaceae, and Alcaligenaceae was peculiar for control offspring. Interestingly, when MIA offspring were treated with a live bacterial strain, Bacteroides (B.) fragilis, fecal levels of the Lachnospiraceae family were restored and, in parallel, several ASD behavioral abnormalities were also normalized (Hsiao et al., 2013).

Further studies by Kim and collaborators have shown that the MIA model is characterized by the presence of IL-17 inducing microbial species that promote Th17 cell differentiation (Kim et al., 2017). Indeed, colonization of pregnant mice with segmented filamented bacteria (SFB) or a mix of human commensal bacteria, known to promote an IL-17 response, led to exacerbated ASD-like phenotypes in MIA offspring, whereas the absence of these microbes limited the effects of MIA (Kim et al., 2017). These data suggest that defined gut commensal bacteria with an ability to promote Th17 cells may increase the risk for NDDs in the

offspring of pregnant mothers undergoing immune system activation (Kim et al., 2017). According to the authors, pregnant women with gut microbial communities that promote excessive Th17 cell differentiation may have an enhanced immune activation and therefore they may have a higher probability to have children developing NDDs symptoms.

How can gut microbiome dysbiosis increase the vulnerability for NDDs?

The precise mechanisms through which the GMB influences brain function and mental health are still under investigation; however, it has been postulated that GMB could influence both physiological and pathological behavioral processes by producing a wide range of bioactive compounds which could influence CNS functions both via systemic circulation and via indirect actions on afferent neuronal routes such as the vagus nerve, or the immune system (Dinan and Cryan, 2017). In this context, several insults, such as inflammatory insults and/or stressful experiences, could modify the GMB composition leading to an imbalance between bacteria with anti-inflammatory and pro-inflammatory properties. An enrichment of bacteria with pro-inflammatory properties causes then a higher gut barrier permeability, which in turn could lead to the passage of both inflammation mediators and bacteria components, including their endotoxins or metabolites, from the gut to the blood circulation and then possibly to the brain (Cattaneo et al., 2017). *Support for this hypothesis stems from several clinical studies investigating blood-based biomarkers of microbial translocation. Specifically, SZ patients exhibit higher serum antibody levels to the fungal pathogens Saccharomyces cerevisiae and Candida albicans (Severance et al., 2015), and soluble CD14 (sCD14) (Severance et al., 2013), a protein marker of bacterial translocation. Elevation of these serological biomarkers suggests increased permeability of the intestinal lumen, or "leaky gut", and is taken as an index of intestinal inflammation (Dickerson et al., 2017). Thus, if the gastrointestinal barrier is compromised, the gut may thus become a source of autointoxication.*

In addition, microbiota colonization of the gut early in life is crucial for the optimal development and function of the immune system, and dysbiosis of the intestinal ecosystem may alter immune responses (Kamada et al., 2013). Specifically, depletion or dysbiosis of microbes that promote development of the immune system may be at the root of a chronic inflammatory state, which can, in turn, influence the CNS functioning (Nguyen et al., 2018). Consequently, chronic inflammation, oxidative stress, and other

physiological dysfunctions that have been implicated in SZ and ASD could be, at least in part, associated with changes in the gastrointestinal microbiome. Furthermore, GMB composition may modulate treatment response and disease remission (Schwarz et al., 2018). This latter finding represents an exciting possibility that the microbiome could be an early indicator of individuals at higher risk for disease progression and an important trait marker that can help to identify at-risk individuals who may benefit from preventive strategies.

All these findings support a probable association between alterations in GMB with SZ and ASD, but heightened efforts are needed to better understand the biological mechanisms involved in the relationship between GMB, inflammation, brain function and NDDs.

3.4 Redox dysregulation/Oxidative stress

Redox signaling plays a key role in several cellular and physiological processes (Jones, 2008) and a modification of this pathway can affect cell proliferation/differentiation, energy metabolism and neurotransmission (Cyr and Domann, 2011; Ray et al., 2012; Valko et al., 2007). Specifically, oxidative stress is defined as an imbalance between anti- (reactive oxygen species (ROS)) and pro-oxidants (reactive nitrogen species (RNS)), resulting in macromolecular damage (Bakunina et al., 2015; Uttara et al., 2009). Recently, oxidative stress has been proposed as a common pathological mechanisms that could lead to the PV+ impairments that are observed in SZ and some forms of ASD (as described in paragraph 3.1.2), and it is thought to be a convergent point of numerous systems that are disrupted in these disorders, such as the glutamatergic, neuroimmune dopaminergic and antioxidant systems (Steullet et al., 2017).

Human studies

Converging data indicate a role for redox deregulation and oxidative stress in the pathophysiology of SZ and ASD (see Table 4) (Anderson and Maes, 2014; Do et al., 2009; Monin et al., 2015). *For example, a novel in-vivo study based on the NAD+/NADH 31P-MRS technique has confirmed redox deregulation in SZ, as the authors uncovered a significant reduction in the NAD+/NADH ratio in chronically ill SZ patients compared to a matched healthy control group (Kim et al., 2017).* Moreover, various studies have observed, under oxidative-stress conditions, reduced levels of glutathione (GSH), the main intracellular non-protein

antioxidant and redox regulator, in the brain (Yao et al., 2004) and peripheral tissues (Gysin et al., 2011) of SZ patients. Similarly, decreased GSH serum levels have also been observed in peripheral blood of ASD subjects (Anderson and Maes, 2014).

Interestingly, Monin and collaborators highlighted the important role of GSH in oligodendrocyte differentiation and myelination processes. They found that GSH levels, measured in the medial PFC of SZ patients, were positively associated with white matter integrity in the cingulum bundle of young healthy subjects and early psychosis patients, leading them to suggest a role for GSH during the development of fibers, either at the level of myelin, axonal size or fiber packing (Monin et al., 2015).

In parallel, various reports suggest that there is a state of enhanced oxidative stress in SZ, which is amplified by increased immuno-inflammatory responses (Anderson et al., 2013). For example, Monji and colleagues (Monji et al., 2013) described a key role of activated microglia in releasing pro-inflammatory cytokines and ROS, leading to abnormal neurogenesis, neuronal degradation, and white matter abnormalities in SZ.

Several lines of evidence have also strongly linked prenatal insults with enhanced oxidative stress. In an interesting in-vitro study, for example, Raciti and colleagues investigated the effects of the synthetic glucocorticoid analog dexamethasone (Dex) on the ROS balance by using the induced pluripotent stem cells (IPSC)-derived lt-NES AF22 cell line, representative of the neuroepithelial stage in the CNS development (Raciti et al., 2016). Prenatal exposure to high levels of glucocorticoids has been indeed shown to have adverse effects on the developing CNS that may lead to alterations in neurogenesis starting from fetal life, resulting in behavioral changes. The results showed an increased intracellular ROS concentration and a concomitant downregulation in the expression levels of four key antioxidant enzymes, namely Catalase, Superoxide Dismutase (SOD) 1, SOD2 and Glutathione Peroxidase (GPX) 7, in "daughter" cells never directly exposed to Dex. The alterations in the intracellular ROS balance was also associated with a decreased neuronal differentiation and a significant downregulation of several neuronal markers, such as the vesicular glutamate transporter 2 (vGLUT2), the glutamic acid decarboxylase 67 (GAD67), the microtubule-associated protein 2 (MAP2), and Doublecortin (DCX). All these findings suggest a direct role played by the increased ROS concentration in the impairment of neuronal differentiation processes that may underlie the onset of both SZ and ASD.

To date, it remains unclear whether alterations in oxidative stress could be mainly due to environmental factors or to a genetic vulnerability, and whether it could be, as mentioned previously, the result of disturbances in glutamatergic, neuroimmune, dopaminergic and antioxidant systems. While extensive effort is being put into answering this question, knowledge acquired so far suggests that antioxidant treatment could be applied to at-risk individuals with the aim of correcting this pathological mark common to a variety of NDDs (Steullet et al., 2017).

Animal studies

The hypothesis that oxidative stress is part of a common pathway leading to inhibitory PV+ abnormalities has been extensively corroborated by animal studies. Indeed, Steullet and collaborators (Steullet et al., 2017) performed a comparative immunohistological analysis of oxidative stress and inhibitory PV+ in the anterior cingulate cortex of several genetic and/or environmental animal models (late adolescent/young adult animals (2-3 months old)) relevant to SZ and ASD. Interestingly, enhanced oxidative stress was observed in all animal models, suggesting, once again, that it could be a consequence of perturbations within different biological systems, including neurotransmission and immunity. This is especially relevant given the reciprocal interactions between these biological systems. Indeed, several proteins related to glutamatergic neurotransmission contain modulatory redox sites (Mustafa et al., 2007). Moreover, while redox state modulates NMDARs function, activation of synaptic NMDARs strengthens neuronal antioxidant defense mechanisms (Hardingham and Bading, 2010). Similarly, oxidative stress is strongly linked to inflammation: many inflammatory mediators are activated by oxidative molecules, while activated immune cells, such as microglia, generate ROS and RNS (Buelna-Chontal and Zazueta, 2013).

Prenatal infections have also been implicated in oxidative stress alterations. In this regard, Stigger and collaborators evaluated the effects of maternal exposure to low doses of LPS, in association or not with perinatal anoxia (PA), in cerebral cortices of newborn pups. The authors found that PA alone increases IL-1 expression levels with no changes in oxidative measures, whereas LPS alone resulted in increased levels of IL-1 and TNFα and this was associated to a high production of free radicals and elevated SOD activity. Furthermore, changes in inflammatory and oxidative stress parameters were even greater when LPS and PA were combined (Stigger et al., 2013). These data support the idea that increased expression of pro-

inflammatory cytokines and free radical levels following prenatal infection might lead to a dysregulation of brain circuit formation, as observed in SZ and ASD.

Similarly, Ginsberg and collaborators used the model of LPS-induced acute maternal inflammation to determine whether the offspring's oxidative state and CRP levels were programmed by gestational inflammation (Ginsberg et al., 2012). The authors found that LPS administration during pregnancy significantly increased the offspring's basal oxidative stress, with a trend toward higher basal serum CRP levels. In response to re-exposure of pups to LPS, CRP levels increased three-fold in the offspring of dams exposed to LPS as compared to offspring of control dams, whereas oxidative stress levels were similar in both groups (Ginsberg et al., 2012). These data suggest that prenatal maternal exposure to LPS increases the baseline levels of oxidative stress and CRP in neonates. Thus, once again, these data support the notion that maternal inflammation may induce long-term alterations in the offspring's immune/inflammatory and oxidative stress response that may predispose to the development of SZ and ASD.

Consistent with the important role of oxidative stress in precipitating the pathological effects of prenatal immune activation, administration of N-acetylcysteine (NAC), a powerful and ubiquitous antioxidant and GSH precursor, to pregnant mice, has been shown to protect the offspring against the detrimental effects of prenatal infection (Lante et al., 2008; Rideau Batista Novais et al., 2013; Swanepoel et al., 2018). For example, in a pioneering study, Lanté and colleagues demonstrated that NAC treatment during pregnancy prevented prenatal LPS effects on cytokine production and hypomyelination as well as on cognitive and neuroplasticity processes (Lante et al., 2008). Specifically, all the effects of LPS, whether in the prenatal or perinatal periods, were completely prevented by pretreatment of the dams with NAC, known to cross the placental barrier (Lante et al., 2008). Similarly, microglial activation and the rapid degeneration of oligodendrocytes progenitors in the brain of in utero LPS-challenged fetuses, as well as the delayed hypomyelinization in the offspring, were largely attenuated when NAC was injected before LPS (Paintlia et al., 2004). These results suggest that the protective effect of NAC may take place within the fetal brain, with a transient decrease of the GSH levels in the hippocampus, which may all be normalized by giving NAC before birth (Lante et al., 2008).

Overall, we can conclude that a proper regulation of the redox system is crucial in controlling PV+ interneuron homeostasis, and plays an important role in the proliferation and the various stages of oligodendrocyte differentiation. Furthermore, abnormal control of the redox system could affect myelination processes and white matter integrity along various neurodevelopmental periods. Adverse and stressful events during early life could affect redox signaling and/or GSH levels and, therefore, could be risk factors for myelin and oligodendrocyte maturation with an impact on later structural connectivity.

4. EPIGENETICS AND NDDs

The potential role of epigenetic deregulation in the pathogenesis of SZ and ASD is a major focus of current research, especially when taking into account the development timeline of such disorders. Indeed, aetiologically relevant environmental insults often occur very early in life, while the pathological phenotype only appears later on. In this context, epigenetic modifications may be critical molecular mechanisms that can translate early insults into long-lasting brain pathology.

Epigenetics, defined as genomic modifications that are heritable during cell division other than the DNA sequence per se (Fakhoury, 2015), represent an important mechanism by which the environment can act on the genome leading to persistent changes in gene expression and/or gene function. Epigenetic modifications include: (i) DNA methylation, which occurs primarily in the context of cytosine-guanine (CpG) dinucleotides (however a significant portion of methylation is found to be positioned at non-CpG sites particularly in neuronal cells (Lister et al., 2013)) and can influence the spatial structure of the DNA and the binding or the repression of specific DNA-binding proteins (Slatkin, 2009), (ii) histone modifications, which influence the condensation of the DNA around histone proteins and regulate the accessibility of functional regions to transcriptional factors (Tordjman et al., 2014) and (iii) post-transcriptional regulation by non-coding RNAs such as microRNAs (miRNAs) (Issler and Chen, 2015; Luoni and Riva, 2016).

4.1 DNA Methylation

Alterations in DNA methylation can, for example, modify the normal development of functional neuronal networks and the differentiation of cells into their normal lineage (Schaevitz and Berger-Sweeney, 2012; Zeisel, 2012) and this has been indeed suggested to underlie the increased risk of developing NDDs

(Kundakovic and Jaric, 2017; Lyall et al., 2014a). In the following paragraphs, we report some of the studies that support the presence of long-lasting alterations in the epigenetic machinery in association with early exposures to stress or infections (see Table 5).

Human studies

Interestingly, individuals affected by SZ or ASD often show altered levels of DNA methylation in several neurodevelopmental genes, such as Spi-1 Proto-Oncogene (SPI1), Interferon Regulatory Factor 8 (IRF8) and Integrin Subunit Beta 2 (ITGB2), that play important roles during microgliogenesis (Kiser et al., 2015; Nardone et al., 2014). Recent studies have also implicated genes that encode molecules participating in the organization and stabilization of pre- and post-synaptic membranes, such as Neurexin 1 (NRXN1) and SH3 And Multiple Ankyrin Repeat Domains 3 (SHANK3) (De Rubeis et al., 2014; Kiser et al., 2015).

One possible mechanism for the long-term effects of prenatal environment is that, once established, aberrant DNA methylation patterns can be passed from one cell generation to another (in immature, still dividing cells), or they are simply stably maintained into adulthood (in mature, post-mitotic neurons), thus providing the mechanism through which the early life environment can exert long-lasting effects on gene expression and phenotype (Kundakovic and Jaric, 2017), and enhance the vulnerability for NDDs later in life and also in the future generations.

Consistent with this hypothesis, human studies indicate a link between prenatal maternal stress/depressive mood and epigenetic changes. *For instance, analysis of cord blood samples from children born to mothers suffering from depression during the third trimester of pregnancy showed the presence of increased DNA methylation of the Nuclear Receptor Subfamily 3 Group C Member 1 (NR3C1) gene, which paralleled increased salivary cortisol stress responses at 3 months of age, as compared to controls (Oberlander et al., 2008).* Interestingly, the effects of maternal stress during pregnancy on NR3C1 DNA methylation in the offspring extend beyond infancy (Radtke et al., 2011), as increased NR3C1 DNA methylation levels were also observed in the whole blood samples of the adolescent offspring. In all these studies, epigenetic changes were present in the offspring's, but not in the maternal blood samples, suggesting that stress-induced epigenetic dysregulation of the NR3C1 gene occurs during developmental epigenetic programming.

Epigenetic alterations have also been observed in peripheral tissues, such as blood leukocytes and epithelial cells, and in post-mortem brains, of SZ and ASD subjects (Fakhoury, 2015; Hannon et al., 2015). For example, distinct methylomic signatures have been observed in the adult brain of patients with SZ, especially in genes associated with fetal brain development (Pidsley et al., 2014). Moreover, Aberg and colleagues uncovered, by performing a methylome-wide association study (MWAS), various differentially methylated sites in the blood of SZ patients that possibly capture signatures of environmental insults (Aberg et al., 2014). These results confirm, once again, that SZ has an important early neurodevelopmental component, and support the notion that changes in epigenetic mechanisms may mediate these effects.

When considering ASD, alterations in the DNA methylation profile of the prefrontal cortex (PFC) (Brodmann Area 10, BA10) and of the anterior cingulate gyrus (Brodmann Area 24, BA24) have been observed in patients as compared to controls (Nardone et al., 2014). In particular, low-density CpG regions, such as intergenic regions, were highly represented among differentially methylated CpGs, whereas high-density CpG regions, such as CpG islands, were less abundant. Interestingly, a gene ontology analysis of the differentially methylated CpG sites in BA10 highlighted the 'immune response' as the most enriched pathway. In addition, the most significant differentially methylated genes, which also showed an inverse correlation with gene expression, were involved both in microglial cell specification and in synaptic pruning during brain development (Nardone et al., 2014), suggesting once again that a dysregulated immune system is one of the biological factors contributing to the pathogenesis of ASD. Importantly, Nardone and colleagues have recently refined these observations by conducting a genome wide methylation study on fluorescence-activated cell sorting (FACS)-sorted neuronal nuclei from the prefrontal cortex, in order to overcome the cellular heterogeneity of the CNS. Interestingly, they uncovered differential DNA methylation patterns in genomic regions enriched in synaptic, GABAergic and immune processes, providing the first characterization of neuronal-specific DNA-methylation changes in ASD (Nardone et al., 2017).

Animal studies

Animal models of NDDs also suggest the involvement of epigenetic modifications. For example, adult mice stressed during the prenatal period recapitulate behavioral deficits similar to those observed in psychotic patients that are associated with specific epigenetic changes. In detail, these animals harbor a significant

increase in DNA methylating enzymes in the promoters of several genes that are associated with SZ, and also with a reduction in the expression of glutamatergic and GABAergic genes (Guidotti et al., 2014) (Table 5).

By using a restraint stress paradigm during pregnancy, Dong and collaborators further demonstrated that prenatal stress reduced cortical and hippocampal mRNA levels of Brain-derived neurotrophic factor (BDNF), a neurotrophin that is crucial for neurodevelopment and synaptic plasticity. These alterations affected brain plasticity, learning, and behavior. Importantly, the authors observed that the decrease in BDNF was accompanied by an increase in DNA methylation and hydroxymethylation within a BDNF regulatory region, suggesting that the changes in the expression levels of the neurotrophin could be due to long-lasting epigenetic alterations. Moreover, these changes were associated, at a behavioral level, with hyperactivity and impaired social interaction, indicating a link between NDD-associated behaviors and epigenetic machinery changes (Dong et al., 2015).

Various studies also report alterations in the epigenome of offspring exposed to prenatal infection (Basil et al., 2014; Labouesse et al., 2015). For example, Basil and colleagues (Basil et al., 2014) reported a significant hypomethylation of the promoter region of the gene coding for methyl CpG binding protein 2 (MeCP2) in the hypothalamus of female offspring prenatally exposed to polyI:C. Similarly, when investigating the effects of polyI:C administered during late gestation, Labouesse and collaborators (Labouesse et al., 2015) found a reduction in the mRNA expression levels of Glutamic acid decarboxylase (GAD)1 and GAD2, encoding GABA-synthesizing enzymes GAD67 and GAD65, respectively. These gene expression changes were accompanied by increased DNA methylation and MeCP2 binding to the GAD1 regulatory region, suggesting, once again, that long-lasting epigenetic changes can mediate long-term molecular deficits, such as GABAergic dysfunction, and possibly underlie the associated altered behavioral and cognitive abnormalities observed in the offspring.

Recently, Richetto and collaborators (Richetto et al., 2017) demonstrated that polyI:C-induced maternal infections leads to persistent genome wide DNA methylation changes at numerous loci and distinct genomic regions. The changes, interestingly, were dependent on the precise timing of the prenatal infection, since the early and late gestational windows clearly differed in terms of the methylation-related epigenetic modifications they induced. In particular, prenatal infection during the late time window of pregnancy

induced methylation changes in genes crucial for GABAergic cell development, such as members of LHX and DLX transcription families (Richetto et al., 2017). On the other hand, early prenatal infection seemed to primarily affect the WNT signaling pathway, which is crucial for the developing nervous system (Richetto et al., 2017). These findings raise the intriguing possibility that prenatal exposure to immune challenges may be one of the environmental factors causing long lasting genome-wide methylation abnormalities observed in NDDs.

Altogether, data from humans and animal models support the hypothesis that environmental factors occurring early in life, especially those with a stress or inflammatory-related component, can alter *in-utero* epigenetic programming, in term of DNA methylation, contributing to neurodevelopmental and behavioral deficits in the offspring.

5. CONCLUSIONS AND PERSPECTIVES

In this review, we have depicted a complex picture illustrating the role of prenatal stress and prenatal infections as main adverse events during neurodevelopment that increase the vulnerability for SZ and ASD by acting on several biological systems, including neurotransmission, inflammation and oxidative stress/redox signaling. We have described, in detail, the alterations in inflammatory-related mechanisms, both in term of peripheral cytokines and chemokines levels, immune cell populations and microglia activation, mainly focusing on the similarities and differences between the two disorders. As interconnected with the immune system, we have also speculated on the possible role of the gut microbiome in the interplay between environment, inflammation and brain development.

By bringing together recent data acquired in this context, our aim was to highlight convergent points of distinct environmental insults and dysregulated systems that could provide common research and therapeutic targets for a wide array of neurodevelopmental disturbances. Among these, the role of the immune system and the GMB in precipitating neurodevelopmental abnormalities in response to early life adversities warrants further examination. Moreover, epigenetic mechanisms have also emerged as a plausible biological substrate through which prenatal environmental exposures can disrupt normal brain development and induce long-lasting effects on brain function and behavior; thus, further efforts should be focused on examining these

mechanisms and their relationship with early life environment. Lastly, as different biological systems play an important role for brain functionality, future studies targeting mediators of these pathways could increase our understanding of the pathophysiology of SZ and ASD and aid in the identification of specific novel targets for future treatment strategies.

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Figure 1: Risk factors occurring early in life that can increase the vulnerability of developing NDDs. Environmental factors, such as stress, infections, alcohol/drug abuse, poor nutrition and/or high fat diet during pregnancy, together with the contribution of the genetic background, can lead to alterations in several biological systems in the offspring.

The normal course of fetal brain development requires a specific balance of cytokines in the maternal and fetal environment. In case of maternal immune response to environmental risk factors, maternal cytokines can cross the placenta and invade the fetal compartments, thus compromising the functional and structural integrity of the developing brain. Changes in neurotransmission between brain areas as well as in microglia activity and in peripheral immunity have been observed in the baby and have been associated with alterations in synaptic plasticity and functionality, possibly contributing to the increased risk for NDDs during childhood.

Table 1: Main findings associated with glutamatergic neurotransmission in animal models and human samples of SZ and ASD.

Table 2: Main findings associated with GABA signaling in animal models and human samples of SZ and ASD.

Table 3: Main findings associated with the immune/inflammatory system in animal models and human samples of SZ and ASD.

Table 4: Main findings associated with redox/oxidative stress system in animal models and human samples of SZ and ASD.

Table 5: Main epigenetic data, in term of DNA methylation, associated with SZ and ASD.

Table 1

Schizophrenia	Autism Spectrum Disorder
Animal models	
Mice lacking mGluR3 have normal PPI and social behaviour but impaired working memory (Fujioka et al., 2014)	Excitatory synapses exhibit a reduced ratio of NMDA/AMPA currents and reduced NMDA receptor expression levels in the mPFC of Mecp2 mutant mice (Sceniak et al., 2016)
PSD95 knock out mice exhibit repetitive behaviour, impaired motor coordination and abnormal social behaviour (Toro and Deakin, 2005)	NMDAR overexpression was reported in Neuroligin (NLGN) mutant mice (Etherton et al., 2011)
Gene expression of multiple AMPA receptor subunits is altered by prenatal influenza infection on E16 (Fatemi et al., 2017), protein expression of GluR1 is reduced in offspring exposed to polyI:C on GD9 (Meyer et al., 2008)	Mice rendered hypoglutamatergic by treatment with MK-801, an NMDA antagonist, showed an impoverishment of the behavioural repertoire (Nilsson et al., 2004)
NMDAR channel binding is increased following polyI:C exposure on GD10 or 19 in the cortex, striatum and hippocampus (Rahman et al., 2017); mGlu-LTD is altered in the rat hippocampus after prenatal immune challenge (Cavalier et al., 2018)	
Prenatal stress reduces glutamate release in the ventral hippocampus of adult rat offspring (Marrocco et al., 2012)	
Prenatal glucocorticoid administration increases protein levels of mGluR1 and decreases Purkinje dendritic growth in the cerebellum of the rat (Pascual et al., 2017)	
Human subjects	
NR1 mRNA expression and protein levels are reduced in dorsolateral prefrontal cortex (DLPFC) of SZ patients compared to controls (Weickert et al., 2013)	Gene expression studies in post mortem brains of ASD patients identified significant increased levels of EAAT1 and AMPA glutamate receptors (GluR1, GluR2, GluR3, GluR4) (Choudhury et al., 2012; Purcell et al., 2001)
PSD95 expression is altered in cortical and hippocampal areas in SZ patients (Toro and Deakin, 2005)	A positive correlation was observed between glutamate receptor interacting protein 1 (GRIP1) and ASD (Mejias et al., 2011)
Identification of two *de novo* mutations in GRIN2A in patients with sporadic SZ (Tarabeux et al., 2011)	Identification of one *de novo* point mutation and protein truncation in GRIN2B in a patient with ASD (Tarabeux et al., 2011)
	Higher plasma glutamate levels in ASD compared with controls (Aldred et al., 2003; Cai et al., 2016; Zheng et al., 2016)
	Serum levels of glutamate were significantly higher in ASD patients as compared to controls (Shinohe et al., 2006)

Table 2

Schizophrenia	Autism Spectrum Disorder
Animal models	
Prenatal stress in mice resulted in changes in the distribution of GAD67(GFP+) GABAergic cells within the dorsal telencephalon of the offspring (Lussier and Stevens, 2016; Stevens et al., 2013)	Mice lacking Mecp2 from GABAergic neurons show numerous autistic features, including repetitive behaviors (Chao et al., 2010)
Prenatal viral like immune activation results in altered promoter methylation of specific GABAergic genes, namely GAD1 and GAD2, in the offspring (Labouesse et al., 2015)	Engrailed (En2(-/-)) mice, which display anatomical, behavioral and clinical "autistic-like" features, show reduced expression of GABAergic marker mRNAs in hippocampus and in prefrontal cortex (Sgado et al., 2013)
Prenatal exposure to immune activation reduces prefrontal mRNA levels of GAD67, α4 and α5, in adult immune-challenged offspring (Richetto et al., 2014)	*The generation of the variety of interneurons appears to be largely dependent on extrinsic influences, including acute or chronic stress (Leto et al., 2012)*
The maturation of prefrontal cortical-accumbens circuits during adolescence is affected in rats with a neonatal ventral hippocampal lesion (NVHL), a model that reflects the periadolescent onset of SZ symptoms. One of the principal elements affected in NVHL rats is the dopamine modulation of prefrontal cortical interneurons (O'Donnell, 2012)	
Human subjects	
GAD67 mRNA levels were lower in SZ post mortem tissues compared to controls (Curley et al., 2011; Davis et al., 2016; Fatemi et al., 2005; Harvey and Boksa, 2012)	GAD67 mRNA levels were lower in ASD post mortem tissues compared to controls (Curley et al., 2011; Davis et al., 2016; Fatemi et al., 2005; Harvey and Boksa, 2012)
Reductions in pre-synaptic GAT1 mRNA levels in the PFC of SZ patients (Lewis et al., 2012)	Data from concentration ligand binding studies indicate that the GABAergic receptor system is significantly reduced in high binding regions, showing an abnormality in the GABA system in ASD (Blatt et al., 2001)
vGAT and GABRA1 mRNA levels were lower in the PFC of the SZ subjects (Fung et al., 2011; Hoftman et al., 2015)	A decrese of 40% GAD67 mRNA expression was observed in Purkinje cells of ASD individuals compared to brain from control subjects (Yip et al., 2007)
Abnormalities in the oscillatory activity at the gamma frequency bands have been suggested to play a key role in the pathophysiology of SZ (Gonzalez-Burgos et al., 2015; Uhlhaas and Singer, 2010)	Reductions of GAD65 and GAD67 proteins were found in parietal cortex and in the cerebellum of ASD brains (Fatemi et al., 2002)
	Despite no baseline differences in the excitatory (E) glutamate and inhibitory (I) GABA system balance, a significant increase in the PFC inhibitory index was observed in response to pharmacologic challenge with riluzole in ASD patients as compared with controls (Ajram et al., 2017)

Table 3

Schizophrenia	Autism Spectrum Disorder
Animal models	
Mouse model exposed to human influenza virus in the first period of pregnancy shows deficits in social interaction, pre-pulse inhibition and exploratory behaviour in the adult offspring (Fatemi et al., 2004; Honda-Okubo et al., 2014; Jurgens et al., 2012; Shi et al., 2003; Xia et al., 2014)	Mouse model exposed to human influenza virus in the first period of pregnancy shows deficits in social interaction, pre-pulse inhibition and exploratory behaviour in the adult offspring (Fatemi et al., 2004; Honda-Okubo et al., 2014; Jurgens et al., 2012; Shi et al., 2003; Xia et al., 2014)
An increase in IL-6 levels alters brain behaviour and development in the offspring (Estes and McAllister, 2016b; Goines and Ashwood, 2013)	An increase in IL-6 levels alters brain behaviour and development in the offspring (Estes and McAllister, 2016b; Goines and Ashwood, 2013)
Administration of LPS or polyI:C to pregnant rodents acutely enhances the levels of pro-inflammatory cytokines in the mother blood, placenta and amniotic fluid and causes microglia activation in the fetal and neonatal brain (Meyer, 2014; Meyer et al., 2005; Saadani-Makki et al., 2008)	Administration of LPS or polyI:C to pregnant rodents acutely enhances the levels of pro-inflammatory cytokines in the mother blood, placenta and amniotic fluid and causes microglia activation in the fetal and neonatal brain (Meyer, 2014; Meyer et al., 2005; Saadani-Makki et al., 2008)
IL-17 acts downstream of IL-6 in mediating the effects of maternal immune activation in several genetic mouse models (Choi et al., 2016)	IL-17 acts downstream of IL-6 in mediating the effects of maternal immune activation in several genetic mouse models (Choi et al., 2016)
When LPS or/and polyI:C are co-administered with antibodies blocking IL-1β or IL-6, the effects of prenatal infection are prevented (Girard et al., 2010; Smith et al., 2007)	When LPS or/and polyI:C are co-administered with antibodies blocking IL-1β or IL-6, the effects of prenatal infection are prevented (Girard et al., 2010; Smith et al., 2007)
Prenatal immune activation negatively affects brain functions and behaviour, such as reduced sociability and increased cued fear expression, in multiple generations (until the third generation) (Weber-Stadlbauer et al., 2017)	Prenatal immune activation negatively affects brain functions and behaviour, such as reduced sociability and increased cued fear expression, in multiple generations (until the third generation) (Weber-Stadlbauer et al., 2017)
Prenatally stressed rodents displayed transient alterations in microglial morphology and an increased release of pro-inflammatory cytokines (Delpech et al., 2016; Gomez-Nicola and Perry, 2015; Roque et al., 2016; Slusarczyk et al., 2015)	Offspring of pregnant dams subjected to daily injections of IL-2 showed ASD-like behaviour. Significant levels of IL-2 were also found in the amniotic fluid and tissues obtained from the same animals (Ponzio et al., 2007)
Long-lasting effects of early life stress were observed in the sensorimotor cortex of adult mice that experienced maternal deprivation (Takatsuru et al., 2015)	Prenatally stressed rodents displayed transient alterations in microglial morphology and an increased release of pro-inflammatory cytokines (Delpech et al., 2016; Gomez-Nicola and Perry, 2015; Roque et al., 2016; Slusarczyk et al., 2015)
Maternal immune activation leads to alterations in the transcriptome and phagocytic activity of microglial cells in the hippocampus of adult male offspring that show a SZ-like (Esslinger et al., 2016; Mattei et al., 2017; Ribeiro et al., 2013; Van den Eynde et al., 2014)	Long-lasting effects of early life stress were observed in the sensorimotor cortex of adult mice that experienced maternal deprivation (Takatsuru et al., 2015)

Alterations in microglial distribution, arborization, cellular stress, and synaptic interactions were found in the hippocampus of male vs. female offspring exposed to polyI:C, with an effect that was accompanied by behavioral impairments, again observed in male animals only (Hui et al., 2018)	Prenatal IL-6 recapitulated prenatal stress-induced changes in adult microglia and the delay in GABAergic progenitor migration (Gumusoglu et al., 2017)
Prenatal IL-6 recapitulated prenatal stress-induced changes in adult microglia and the delay in GABAergic progenitor migration (Gumusoglu et al., 2017)	
Human subjects	
multiple molecules with potent anti-inflammatory and immunosuppressive properties such as IL-10, TGF-β, soluble IL-1 receptor antagonist (sIL-1RA), and soluble TNF receptor (sTNF-R) are increased in SZ subjects (Maes et al., 2002; Numata et al., 2008; Potvin et al., 2008)	Increased production of TGF-α1, TNFα, IL-6 and IL-10 is observed in brain and in blood samples of ASD subjects (Ross et al., 2013)
IL-2, sIL-2R, IL-6 and IL1-RA are correlated to negative symptomps and duration of SZ (Asevedo et al., 2014; Hope et al., 2013; Kim et al., 2000)	Increased serum levels of MCP-1 and decreased levels of RANTES were identified in ASD subjects as compared to controls (Zerbo et al., 2014)
Worse cognitive performance in SZ patients were correlated with higher CRP levels, whereas less consistent evidence suggested better cognitive functioning of SZ patients with higher levels of TNF-α (Misiak et al., 2017)	Lower plasma levels of TGF-β1 were found in children with ASD as compared with controls and with children with other disabilities (Ashwood et al., 2008)
Increased serum levels of the pro-inflammatory cytokine IL-6 was associated with 2-fold increase risk of developing a psychiatric disorder including SZ at age 18 (Khandaker et al., 2015)	Increased plasma levels of MCP-1, RANTES and eotaxin were identified in ASD children as compared to controls and to children with other disabilities (Ashwood et al., 2011a)
An increased risk of late SZ onset was associated with increased serum CRP levels (Wium-Andersen et al., 2014)	IL-1β, IL-6, IL-8, IFNγ, eotaxin and MCP-1 wer significantly higher in ASD subjects compared with controls, while TGF-β1 were significantly lower (Madore et al., 2016; Masi et al., 2015)
Identification of lower TNF-α levels in serum of chronic SZ patients (Hope et al., 2013; Lv et al., 2015)	Increased levels of IL-6, TFN-α and decreased diurnal variation of cortisol were identified in blood samples of ASD patients as compared to controls (Yang et al., 2015)
A decrease in IL-2 mRNA levels and an increase in serum IL-6, IL-8 and TNF-α protein levels were found in SZ subjects compared to controls (Boerrigter et al., 2017)	A nearly 50-fold increase in TNF-α level was found in the cerebrospinal fluid (CSF) of ASD children (Chez et al., 2007)
Increased levels of CCL11, CCL3, sTNF-R1 and sTNF-R2 and decreased levels of CXCL10, TNF-α, IL-2 and IL-4 were found in SZ patients as compared to controls (Noto et al., 2015)	Compared to healthy controls, ASD patients had increased percentages of CD8(+) T-cells and B-cells, and a decrease in the percentage of NKT cells (Ashwood et al., 2011b; Lopez-Cacho et al., 2016)

Higher levels of IL-1β, IL-6 and TNF-α were identified in blood of SZ patients at the onset of the disorder as compared to matched controls (Di Nicola et al., 2013; Miller et al., 2011; Mondelli et al., 2011; Song et al., 2013b)	ASD patients in comparison to controls have a diminished Th2 anti-inflammatory response and an increased Th1 pro inflammatory cytokine response, as increased levels of IFNγ and IL 1RA, resulting in a Th1 skewing (Bjorklund et al., 2016; Croonenberghs et al., 2002; Goines et al., 2011)
Increased number of T lymphocytes (CD3+), T helper cells (CD4+) and a higher ratio between T helper and T cytotoxic cells (CD4+/CD8+) was reported in drug-naïve SZ patients. A higher proportion of T helper CD4+ and Natural Killer CD56+ cells was observed in acutely relapsed SZ patients (Miller et al., 2013)	ASD children showed significantly reduced levels of plasma IgG and IgM compared to children with other disabilities and controls (Heuer et al., 2008)
Activation of microglia and astrocytes have been associated with SZ (Patterson, 2009)	A shift in the immunoglobulin composition in serum, with low normal IgA and CD23 expressing B cells, was observed in ASD, particularly in children with regressive ASD (Wasilewska et al., 2012)
A reduction in the number of NK cells was observed in SZ patients (Karpinski et al., 2016)	Several ligands of CCR4, such as CCL22 and CCL17, were reported to be elevated in ASD patients (Al-Ayadhi and Mostafa, 2013)
HLA-DR immunoreactive microglia positive cells were found in SZ patients but not in controls (Bayer et al., 1999; Fillman et al., 2013a; Garey, 2010; Radewicz et al., 2000; Wierzba-Bobrowicz et al., 2005)	NK cells were higher in children diagnosed with ASD as compared to controls (Bressler et al., 2012; Enstrom et al., 2010)
No differences in HLA-DR activated microglia were observed in the PFC, anterior cingulated cortex, hippocampus and medio dorsal nucleus of the thalamus in SZ patients as compared to controls (Steiner et al., 2006). Only suicide was associated with higher HLA-DR positive cells (Steiner et al., 2008)	Activation of microglia causes an increase in nitric oxyde (NO) that leads to a decrease in NK cell function (Enstrom et al., 2009; Takano, 2015)
INF-γ, IL-1β, TNF-α and TNF-α receptor 1 mRNA and protein levels have been found increased in the PFC of SZ patients compared to unaffected controls (Dean et al., 2013; Harris et al., 2012; Trepanier et al., 2016)	Activation of microglia and astrocytes have been associated with ASD (Morgan et al., 2010; Schumann and Amaral, 2006; van Kooten et al., 2008)
A microarray analysis found a decrease in IL-8 and IL-1α mRNA levels in the temporal cortex of SZ patients as compared with controls, although microarray results were not validated by qPCR (Schmitt et al., 2011)	Altered microglial profile and increased levels of inflammatory cytokines such as IFN γ, IL 1β, IL 6, TNF α and chemokines CCL 2 were found in the post-mortem brain tissue of individuals diagnosed with ASD (Garbett et al., 2008; Morgan et al., 2010)
A decrease in IL-8 mRNA levels was found in the middle frontal gyrus of SZ subjects, whereas IL-1β, TNF-α, IL-18 and IL-6 were not changed (Fillman et al., 2014)	In vivo studies have identified excessive microglial activation in multiple brain regions in young adult subjects with ASD as compared to controls (Suzuki et al., 2013)
Two microarray studies found a decrease in CCL3 and in IL-13RA expression levels in the prefrontal cortex and in the temporal lobe of SZ patients (Durrenberger et al., 2015; Nakatani et al., 2006)	

In vivo studies have identified higher microglial activation in SZ patients as compared to controls (Bloomfield et al., 2016; Doorduin et al., 2009; van Berckel et al., 2008)	
No differences in microglia activation, both in gray and white matter brain regions, were found between SZ patients and controls (Kenk et al., 2015; Notter et al., 2017)	
A longitudinal 10-year prospective cohort study showed that experiences of childhood trauma and recent life events are strongly correlated and interacted additively in increasing the risk of psychosis (Lataster et al., 2012)	
DNA of Chlamydophila was found 4 times higher in brain samples of SZ patients than in controls (Fellerhoff and Wank, 2011)	

Table 4

Schizophrenia	Autism Spectrum Disorder
Animal models	
Relative to their control mice, adult mice with the human 15q13.3 deletion (Df[h15q13]/+) showed increased oxidative stress (+262% 8-oxo-dG immunolabeling intensity) (Steullet et al., 2017)	Relative to their control mice, adult mice with the human 15q13.3 deletion (Df[h15q13]/+) showed increased oxidative stress (+262% 8-oxo-dG immunolabeling intensity) (Steullet et al., 2017)
Relative to their control WT mice, GRIN2A KO mice display no significant oxidative stress. However, when an additional oxidative challenge was applied during early postnatal development (from days 10 to 20), young adult GRIN2A KO mice showed significant oxidative stress (+159% relative to WT) (Steullet et al., 2017)	Relative to their control WT mice, GRIN2A KO mice display no significant oxidative stress. However, when an additional oxidative challenge was applied during early postnatal development (from days 10 to 20), young adult GRIN2A KO mice showed significant oxidative stress (+159% relative to WT) (Steullet et al., 2017)
Relative to their control WT, young adult GCLM KO mice with a functional deletion of the modulatory subunit of the GSH synthesizing enzyme showed oxidative stress (+53% 8-oxo-dG immunolabeling intensity) (Steullet et al., 2017)	Relative to their control WT, young adult GCLM KO mice with a functional deletion of the modulatory subunit of the GSH synthesizing enzyme showed oxidative stress (+53% 8-oxo-dG immunolabeling intensity) (Steullet et al., 2017)
Combining prenatal immune challenge (at embryonic day E9) using the viral mimetic polyI:C with sub-chronic unpredictable stress during pubescence (postnatal days 30–40) increased the oxidative stress levels (+190%) (Steullet et al., 2017)	Combining prenatal immune challenge (at embryonic day E9) using the viral mimetic polyI:C with sub-chronic unpredictable stress during pubescence (postnatal days 30–40) increased the oxidative stress levels (+190%) (Steullet et al., 2017)
Adult mice with the human 1q21 deletion (Df[h1q21]/+) did not show any significant oxidative stress as compared to their control adult mice (Steullet et al., 2017)	In adult FMR1 KO mice, a strong increase in oxidative stress (+307% 8-oxo-dG immunolabeling intensity) was observed in comparison to their WT controls (Steullet et al., 2017)
An increase in intensity of 8-oxo-dG immunoreactivity (+410%) was identified in SRR KO mice as compared to their WT controls (Steullet et al., 2017)	*The effects of maternal exposure to low doses of bacterial endotoxin (lipopolysaccharide, LPS) associated or not with perinatal anoxia (PA) in oxidative and inflammatory parameters were examined in cerebral cortices of newborns pups. Data showed that changes on inflammatory and oxidative stress parameters were even greater when LPS and PA were combined (Stigger et al., 2013)*
Adult mice with the human 22q11.2 deletion (LgDel/+) displayed higher oxydative stress (+125% 8-oxo-dG immunoreactivity intensity) as compared to their control WT mice (Steullet et al., 2017)	*LPS administration during pregnancy significantly increased the offspring's basal oxidative stress, with a trend toward higher basal serum CRP levels. In response to re-exposure of pups to LPS, CRP levels increased three-fold in the offspring of dams exposed to LPS as compared to offspring of control dams, whereas oxidative stress levels were similar in both groups (Ginsberg et al., 2012)*

In young adult NVHL rats, a strong increase of 8-oxo-dG immunolabeling intensity (+450% relative to control sham rats) was observed (Steullet et al., 2017)	*Administration of N-acetylcysteine (NAC), a GSH precursor, to pregnant mice prevented prenatal LPS effects on cytokine production and hypomyelination as well as on cognitive and neuroplasticity processes (Lante et al., 2008; Rideau Batista Novais et al., 2013; Swanepoel et al., 2018). This is largely attenuated when NAC is injected before LPS (Paintlia et al., 2004)*
Prenatal administration of MAM recapitulates in an increase of 8-oxo-dG immunolabeling intensity (+164%) in MAM relative to their control rats (Steullet et al., 2017)	
The effects of maternal exposure to low doses of bacterial endotoxin (lipopolysaccharide, LPS) associated or not with perinatal anoxia (PA) in oxidative and inflammatory parameters were examined in cerebral cortices of newborns pups. Data showed that changes on inflammatory and oxidative stress parameters were even greater when LPS and PA were combined (Stigger et al., 2013)	
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Human subjects	
Decreased GSH levels were found in CSF and in medial PFC of SZ subjects (Do et al., 2009; Monin et al., 2015; Yao et al., 2004)	Decreased GSH levels were found in resting peripheral blood mononuclear cells, activated CD4+ T cells and monocytes as well as in the serum of ASD children (Anderson and Maes, 2014; Rose et al., 2012)
High-risk genotype SZ patients, as compared with low risk individuals, had decreased fibroblast GSH levels (Gysin et al., 2011; Monin et al., 2015)	ASD subjects showed significantly decreased plasma GSH, cysteine, taurine, sulfate, and free sulfate levels as compared to controls (Geier et al., 2009)
A significant decrease of GSH was found in post-mortem caudate from SZ patients as compared with control subjects without any psychiatric disorders (Yao et al., 2006)	Synaptic NMDAR activity enhances antioxidant defences which contributes to neuroprotection against oxidative insults (Hardingham and Bading, 2010)
Synaptic NMDAR activity enhances antioxidant defences which contribute to neuroprotection against oxidative insults (Hardingham and Bading, 2010)	*An increased intracellular ROS concentration and a concomitant downregulation in the expression levels of four key antioxidant enzymes, CATALASE, SOD1, SOD2 and GPX7 were found in "daughter" cells never directly exposed to dexamethasone (Dex). The alterations in the intracellular ROS balance was also associated with a significant downregulation of several neuronal markers (Raciti et al., 2016)*

A significant reduction in the NAD+/NADH ratio was observed in chronically ill SZ patients as compared to a matched control group (Kim et al., 2017)	
A state of enhanced oxidative stress which is amplified by increased immune-inflammatory responses was observed in SZ patients (Anderson et al., 2013; Monji et al., 2013)	
An increased intracellular ROS concentration and a concomitant downregulation in the expression levels of four key antioxidant enzymes, CATALASE, SOD1, SOD2 and GPX7 were found in "daughter" induced pluripotent stem cells never directly exposed to dexamethasone (Dex). The alterations in the intracellular ROS balance was also associated with a decreased neuronal differentiation and a significant downregulation of several neuronal markers (Raciti et al., 2016)	

Table 5

Schizophrenia	Autism Spectrum Disorder
Animal models	
The adult brain of the offspring of dams stressed during pregnancy is characterized by a significant increase in DNMT1, TET1, 5-methylcytosine and 5-hydroxymethylcytosine at SZ candidate gene promoters, and by a reduction in the expression of glutamatergic and GABAergic genes (Guidotti et al., 2014)	Prenatal infection during late pregnancy induced methylation changes in genes crucial for GABAergic cell development, including members of LHX and DLX transcription families. Early prenatal infection primarily affected the WNT signaling pathway, which is crucial for the developing nervous system (Richetto et al., 2017)
A significant increase in DNMT1 and TET1 and a significant decrease in BDNF variants were identified in the frontal cortex and in the hippocampus of adult offspring of pregnant mice subjected to prenatal stress. The decrease of corresponding BDNF transcript levels was associated to an enrichment of 5-methylcytosine and 5-hydroxymethylcytosine levels at BDNF gene regulatory regions (Dong et al., 2015)	
A significant global DNA hypomethylation and a significant hypomethylation of the promoter region of MECP2 were identified in the hipotalamus of female offspring prenatally exposed to polyI:C (Basil et al., 2014)	
Prenatal immune activation increased prefrontal levels of 5-methylcytosine and 5-hydroxymethylcytosine in the promoter region of GAD1 and GAD2, encoding GABA-synthesizing enzymes GAD67 and GAD65 respectively. These gene expression downregulation was also accompained by increased DNA methylation and MeCP2 binding to the GAD1 and GAD2 regulatory region (Labouesse et al., 2015)	
Human subjects	
A large (approximately 8 kb) region spanning the Neuritin 1 (NRN1) gene across which 29 adjacent CpG sites was consistently hypomethylated in SZ patients compared with controls (Pidsley et al., 2014)	In Brodmann area 10 (BA10) of ASD subjects a very significant enrichment for genomic areas responsible for immune functions was found among the hypomethylated CpGs, whereas genes related to synaptic membrane were enriched among hypermethylated CpGs (Nardone et al., 2014)
DNA methylation biomarkers were identified in blood samples from SZ patients as compared to controls. The top methylated region was located in FAM63B, and it was part of the networks regulated by miRNAs involved in neuronal differentiation and dopaminergic gene expression. Many other top methylated regions could be linked to hypoxia and to infections. A site in RELN, one of the most frequently studied candidates in methylation studies of SZ, was also identified (Aberg et al., 2014)	58 differentially methylated regions (DMRs) that included loci associated to GABAergic system genes, particularly ABAT and GABBR1 and brain-specific miRNAs were identified by using a genome-wide methylation study on fluorescence-activated neuronal nuclei from the frontal cortex of 16 male ASD and 15 male control subjects (Nardone et al., 2017)

	De novo loss-of function mutations in over 5% of ASD subjects were identified in genes implicated in histone post-translational modifications involving lysine methylation/demethylation (De Rubeis et al., 2014)
	ASD is associated with an increase in overall DNA methylation of SHANK3, a gene involved in the synapse formation (Zhu et al., 2014b)