Review article

The impact of (ab)normal maternal environment on cortical development

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ABSTRACT

The cortex in the mammalian brain is the most complex brain region that integrates sensory information and coordinates motor and cognitive processes. To perform such functions, the cortex contains multiple subtypes of neurons that are generated during embryogenesis. Newly born neurons migrate to their proper location in the cortex, grow axons and dendrites, and form neuronal circuits. These developmental processes in the fetal brain are regulated to a large extent by a great variety of factors derived from the mother - starting from simple nutrients as building blocks and ending with hormones. Thus, when the normal maternal environment is disturbed due to maternal infection, stress, malnutrition, or toxic substances, it might have a profound impact on cortical development and the offspring can develop a variety of neurodevelopmental disorders. Here we first describe the major developmental processes which generate neuronal diversity in the cortex. We then review our knowledge of how most common maternal insults affect cortical development, perturb neuronal circuits, and lead to neurodevelopmental disorders. We further present a concept of selective vulnerability of cortical neuronal subtypes to maternal-derived insults, where the vulnerability of cortical neurons and their progenitors to an insult depends on the time (developmental period), place (location in the developing brain), and type (unique features of a cell type and an insult). Finally, we provide evidence for the existence of selective vulnerability during cortical development and identify the most vulnerable neuronal types, stages of differentiation, and developmental time for major maternal-derived insults.

1. Introduction

The mammalian brain is organized into numerous anatomical regions that interconnect to control complex behavioral traits. Among them, the neocortex (termed “cortex” hereafter in the text) is a recently evolved, six-layered structure with regional specialization (e.g., visual, motor, auditory, associative etc.) that processes incoming sensory information, integrates multiple sensory inputs, and instructs behavioral output (Molnár et al., 2019; Shipp, 2007). Such a multilayer cortical structure is a unique feature of mammals and underlies their highly complex cognitive abilities. Activity in the cortex is regulated by complex interactions between the excitatory glutamatergic principal neurons and inhibitory GABAergic interneurons, where the former are organized into layers and the latter are sparsely distributed, usually with some preference for particular layers (Ascoli et al., 2008; Yuste et al., 2020). Both principal neurons and GABAergic interneurons can be divided into multiple subtypes, >100 in human cortex, based on their laminar position, transcriptomic identity, and functional and morphological properties (Gouwens et al., 2020; Scala et al., 2020; Yuste et al., 2020). Thus, the cortex represents the most complex brain region. Such complexity is created during brain development, and the resulting structure of the cortex represents the outcome of multiple genetic and environmental factors taking course during development. Multiple maternal factors reach the developing embryo via placenta or blood and control cell proliferation, migration, differentiation, maturation, and survival/death. However, at the same time, a huge body of evidence shows how abnormal maternal environment leads to impaired cortical development and, as a result, gives rise to neurodevelopmental disorders, such as schizophrenia, autism, epilepsy, and others (Estes and McAllister, 2016; Schmitt et al., 2014; Van den Bergh et al., 2018). Given the complexity of cortical development, different maternal insults could produce a variety of phenotypes that should depend on the type of insult and period of development. In the sections below, we will first provide an overview of normal cortical development and then focus on the effect of maternal-derived insults. We emphasize differential susceptibility of cortical cell types to various maternal-derived insults that depends on space and time. Furthermore, we define the concept of selective vulnerability in the context of maternal-derived insults and...
provide data supporting the concept. Importantly, it should be noted that although the focus of the review is on the cortex, other brain regions, including the amygdala, thalamus, cerebellum, brainstem, etc, can be affected by the same mechanisms we describe here.

2. Cortical development

2.1. Overview of cortical development: from anterior neural tube to multi-layered cortex

The cortex derives from the anterior-most part of the developing neural tube, which is first patterned to the forebrain and then to the telencephalon (Fig. 1A,B) (Ericson et al., 1997; Mangale et al., 2008; Monuki and Walsh, 2001). Forebrain identity is mainly driven by the expression of early transcription factors Six3 and Foxg1 in the anterior neural tube (Lagutin et al., 2003; Shimamura and Rubenstein, 1997; Tao and Lai, 1992), and further regionalization of the telencephalon occurs by the combinatorial expression of Emx2, Pax6, Gsx2, and Nkx2.1 transcription factors. These factors divide the telencephalic germinal zone into dorsal, lateral, and ventral identities (Bishop et al., 2002; Corbin et al., 2002; Muzio et al., 2002; O’Leary and Sahara, 2006; Stoykova et al., 1996; Susel et al., 1999; Visel et al., 2013). The dorsal telencephalon gives rise to the layers of principal neurons in the cortex, whereas the ventral part produces GABAergic interneurons (Fig. 1C).

The regionalization and molecular specification of the ventral telencephalon is further controlled by the expression of a set of transcription factors, such as members of the Dlx family (Dlx1/2 and Dlx5/6), Olig1/2, and Mash1 (Alzu’bi et al., 2016; Cobos et al., 2006; Miyoshi et al., 2007; Silbereis et al., 2014).

The germinal zone that generates all cortical neurons is located around the brain ventricles. Early neural stem cell-like neuroepithelial cells (in rodents at embryonic days E8.5-E9.5, in humans at gestational weeks GW8-GW10) undergo repeated cycles of symmetric divisions prior to remodeling to the neuron producing radial glial progenitor cells (RGCs) (Fig. 1D, D’) (Aaku-Saraste, 1996; Aaku-Saraste et al., 1997; Eze et al., 2020). The RGCs of the dorsal telencephalon produce the bulk of cortical principal neurons by direct or indirect divisions (Anthony et al., 2004; Malatesta et al., 2000; Nowakowski et al., 2018; Williams and Price, 1995). RGCs exist as morphologically distinct subtypes (Betzeau et al., 2013; Gal et al., 2006; Noctor et al., 2002; Pollen et al., 2015; Rakic, 1974) and can be differentiated according to their cell-biology and gene-expression profiles (Kriegstein and Alvarez-Buylla, 2009; Pollen et al., 2015, 2014). During early neurogenesis, RGCs undergo asymmetric divisions to self-renew and to produce neurons (Fig. 1D, D’), whereas at later stages, they increasingly shift to neurogenic divisions (Miyata et al., 2001; Noctor et al., 2001; Ostrem et al., 2014), before culminating in the production of glial cells such as astrocytes and oligodendrocytes (Kessaris et al., 2006; Malatesta et al., 2000; Williams and Price, 1995). One particular type of progenitors, the outer radial glial cells (oRGCs), is largely amplified in higher mammals (Fig. 1D, D’), e.g., humans, and has been proposed to undergo cortical expansion in their brains (Fietz et al., 2010; Pollen et al., 2015). The oRGCs share several similarities with late RGCs, including transcriptional signatures, self-renewing, and neuronal differentiating divisions (Garcia-Moreno et al., 2012; Kelava et al., 2012; Pollen et al., 2015).

The earliest steps in cortical development include formation of the preplate, which then splits into the cortical plate, subplate, and intermediate zone (Fig. 2). The very first neurons of the human cortex arrive tangentially from outside the cortex, the subpallium region (Bystrom et al., 2006), followed by the onset of local cortical neurogenesis to generate principal neurons. Layers of principal neurons are developed in the cortical plate and they are produced in an inside-out fashion, i.e., first the deepest layer is generated and neurons for each consecutive layer migrate further above pre-existing layers (Fig. 2). Thus, precise neuronal migration is an important process for the formation of layers of cortical principal neurons. Newly born principal neurons utilize the pial-directed process of RGCs that provide a migration scaffold (Fig. 1D, D’) (Miyata et al., 2001; Noctor et al., 2001; Rakic, 1972). In addition, the migration is controlled by cell-to-cell interaction between these neurons and their progenitors (Parthasarathy et al., 2014).

Post-mitotic principal neurons develop functional circuits over a protracted period, and the timing depends on the cortical region. During this period, neurons mature morphologically and electrophysiologically, which is regulated by the expression of specific ionic channels as well as local and global neuronal activity (Kroon et al., 2019). The subplate plays a major role in early organization of cortical circuitry (Fig. 2). The subplate contains neurons that are born both locally and in surrounding regions (Hoerder-Suabedissen and Molnár, 2013; Pedraza et al., 2014). The subplate expands dramatically during mid-human corticogenesis and establishes temporal neuronal circuits, shrinking before birth, with layer 6b and white matter interstitial neurons being the remnants of the subplate in the postnatal brain (Molnár et al., 2020). Finally, a large number of cortical principal neurons die before complete maturation, and it has been proposed that their survival depends on successful integration in the circuits, i.e., activity-dependent survival (reviewed in Pfisterer and Khodosevich, 2017).

In contrast to principal neurons, cortical GABAergic interneurons arise from the ventral parts of the telencephalon in specialized structures called ganglionic eminences (GEs) (Fig. 1E). In the rostral-developing telencephalon, a shallow sulcus separates the GE into medial and lateral parts (MGE and LG, respectively), while no such sulcus exists for the caudal part (CGE). Of these, only the MGE and CGE produce GABAergic interneurons destined for the cortex while the LGE gives rise to striatal and olfactory bulb interneurons (Bartolini et al., 2013). Neuroblasts then migrate tangentially from the GEs towards the cortical plate (Fig. 1C) in response to chemotactic signals coming from intermediate progenitors, subplate neurons, and Cajal-Retzius cells (Abé et al., 2015; Sessa et al., 2010). Once in the cortical plate, they switch to a radial migratory pattern, moving either dorsally or ventrally to disperse in the cortical layers and reach their final position (Miyoshi and Fishell, 2011). Subsequently, a significant proportion of cortical interneurons undergo programmed cell death (Southwell et al., 2012; Wong et al., 2018), while the surviving interneurons mature over two to three months in mice.

The comparative timeline and milestones of cortical development for rodent and human cortex are shown in Fig. 1F.

2.2. The diversity of cortical neuronal subtypes and how the diversity is established

Mature cortical circuits are highly complex (Fig. 2), and neurons within cortical circuits are classified on the basis of several distinct features, such as morphology, laminar positioning, connectivity, physiological characteristics, and gene expression (Fig. 3A-E) (Molyneaux et al., 2007; Tremblay et al., 2016; Yuste et al., 2020). With regards to principal neurons, the output region of the neuron is frequently used as the first-order classification. Thus, principal neurons are subdivided into commissural, corticofugal, and associative neurons (Fame et al., 2011; Molyneaux et al., 2007). Briefly, commissural neurons (also called callosal projection neurons) are largely found in upper cortical layers (Molyneaux et al., 2007) and send axonal projections to the contralateral cortex. In contrast, the corticofugal neurons are located in the deeper cortical layers and their axons project to the thalamic nuclei (Higashi et al., 2005; Hoerder-Suabedissen et al., 2018; Hoerder-Suabedissen and Molnár, 2013; McConnell et al., 1989; Molnár et al., 1998) or to extracortical target areas in the midbrain, hindbrain, and spinal cord (Arletta et al., 2005; Greig et al., 2013). Finally, associative neurons project unilaterally, thus targeting cortical neurons within the same hemisphere (MacDonald et al., 2018; Mitchell and Macklis, 2005). Over the last 20 years, a number of genes have been specified that control the identity and connectivity of different principal neuron subtypes (reviewed in Greig et al., 2013). These efforts culminated in several
Fig. 1. Overview of cortical development.

A) During early development, the neural tube is progressively subdivided into the forebrain (green), midbrain (yellow) and hindbrain (orange) by the action of patterning factors.

B) Later during development, the forebrain is further subdivided into the telencephalon (dark green) and diencephalon (light green), the midbrain transforms into the mesencephalon, whereas the hindbrain differentiates into the more rostral metencephalon (orange) and the caudal myelencephalon (red). The telencephalon will develop into the cerebral cortex during the course of development.

C) In the middle panel, the rodent telencephalon at midgestation; on the left and right, two coronal sections at different anterior-posterior levels are shown. Inhibitory GABAergic interneurons are generated in the lateral, medial and caudal ganglionic eminences (LGE, MGE and CGE respectively). Newly born inhibitory neurons generated in the MGE (blue) and CGE (orange) migrate tangentially to the cortex, whereas those generated in the LGE (blue) migrate to the striatum and olfactory bulb.

Excitatory principal neurons are generated by the dorsal germinal zone (magenta) and migrate radially outwards into the developing cortex. Two side arrows in the right panel indicate early populations of excitatory principal neurons that are generated outside of the developing cortex.

D and D') Schematic representation of the dorsal germinal zone showing the generation of excitatory principal neurons in mouse and human brain, respectively. Neuroepithelial cells are early progenitor cells that are located in the ventricular zone (VZ) and they differentiate into radial glial progenitor cells (RGCs, green with long process) at the early stages of cortical development. RGCs first undergo symmetric divisions to self-renew and directly generate neuroblasts. Later during development, RGCs switch differentiation mode and produce intermediate progenitor cells (IPCs, green with round shape) that in turn generate neuroblasts. A particular type of RGCs, outer RGCs (oRGCs), lose their apical process, detach from the ventricle and translocate to the subventricular zone (SVZ). These oRGCs reside in the outer SVZ (OSVZ) and rapidly divide to produce IPCs and neuroblasts. The OSVZ and inner SVZ (ISVZ) division is present in human, but not in mouse brain, and the OSVZ with oRGCs were proposed to contribute to a large expansion of the cortex in higher mammals. Neuroblasts migrate along the RGC processes towards the marginal zone (MZ) and detach in the cortical plate (CP) to mature into cortical principal neurons (light blue).

E) Schematic representation of the ventral germinal zone showing the generation of GABAergic neurons in mouse and human brain, respectively. RGCs (dark blue with long process) are situated in the VZ and undergo asymmetric divisions to generate either IPCs (dark blue with round shape) or neuroblasts (dark red). The IPCs in turn undergo terminal differentiation and generate neuroblasts, which either migrate through the SVZ to the cortex or first migrate along the RGC processes towards the outer brain surface and then along it to the developing cortex, as shown by the blue and orange arrows in the Fig. 1C. Note that, similar to the dorsal germinal zone, human SVZ in the MGE/CGE is divided into the OSVZ and ISVZ, and the OSVZ contains a large number of oRGCs (human version is not shown in the figure).

F) Milestones of cortical development showing the comparison between mouse (upper part) and human (lower part) timelines.

SST interneurons, whereas inhibitor of differentiation 2 (ID2)-expressing interneurons are mainly located in L1-L2 and inhibit principal neurons at their dendrites.

Fig. 2. Cortical layer formation and scheme of typical cortical circuit showing laminar distribution of major neuronal cell types in the mature cortex.

During the earliest steps in cortical development, the preplate (PP) is formed, which later splits into the cortical plate (CP), subplate (SP), and intermediate zone (IZ). Layers of principal neurons are generated in the CP in an inside-out fashion. By the time of birth, the SP and most of VZ/SVZ is replaced by the white matter (WM). Principal neurons (red) are distributed across the layers 2 and 6 (L2-L6) and project to different cortical, subcortical and spinal regions. In contrast, GABAergic interneurons (green) are projecting mainly locally and inhibit principal neurons at different cellular compartments. For instance, parvalbumin (PV)-expressing basket interneurons exert perisomatic inhibition while PV chandelier cells inhibit principal neurons at the axon initial segment. In contrast, somatostatin (SST)-expressing interneurons target the dendrites of principal neurons in L1. Other interneurons such as vasoactive intestinal peptide (VIP)-expressing interneurons inhibit both PV and
Fig. 3. The diversity of neuronal subtypes in the cortex.
Five major parameters that are utilized to characterize the diversity of cortical neurons.
A) Layer position. Neuronal subtypes are differentially clustered into layer positions based on their function, e.g. corticofugal principal neurons are enriched in deeper layers (L5-L6) and commissural neurons are enriched in superficial layers (L2-L3). Principal neurons are in red, GABAergic interneurons are in green.
B) Morphology. Major morphologies for principal neurons (red) and GABAergic interneurons (green) are presented. For principal neurons, only dendrites are shown and for GABAergic interneurons both dendrites (dark green) and axons (light green) are shown. Note that while specific morphologies of principal neurons are well correlated with layer-wise position, such correlation for GABAergic interneurons is much less strong and most morphological types of GABAergic interneurons are spread across several layers. Neuronal traces are reproduced from (Radnikow and Feldmeyer, 2018) and (Laturnus et al., 2019).
C) Connectivity. Subtypes of GABAergic interneurons can be differentiated on the basis of their targeting of principal neurons. Thus, GABAergic interneurons could target the soma (e.g. basket cells), axon initial segment (e.g. chandelier cells) and dendrites (e.g. Martinotti cells) of the principal neurons.
D) Physiology. Neuronal subtypes can be differentiated based on their action potential firing patterns. Traces are reproduced from (Gouwens et al., 2019) and represent both principal neurons and interneurons.
E) Gene expression. UMAP plot showing neuronal subtypes in the prefrontal human cortex based on single-cell transcriptomics. Smaller UMAP plots on the right represent marker expression for major families of principal neurons (top 4) and GABAergic interneurons (bottom 4). Graphs are reproduced from (Batiuk et al., 2020).
A, from top to bottom: Dorsal radial glia progenitor cells, intermediate progenitor cells, migrating neuroblasts and mature neurons. To be expressed as early as E10.5 (Puelles et al., 2016). In contrast to principal neurons, mature interneuron marker expression cannot be discerned until postnatal stages with the exception of Sst that begins to be expressed as early as E10.5 (Puelles et al., 2016).

Fezf2, Ctip2 and Sox5 specify corticofugal connectivity and Satb2, Ctip2 and Cux2 instruct intracortical connectivity. On the other hand, interneuron progenitors express different Tfs depending on their regional identity. As a result, MGE and CGE progenitors can be differentiated by the expression of Nkx2.1 and COUP-TFII, respectively. In contrast to principal neurons, mature interneuron marker expression cannot be discerned until postnatal stages with the exception of Sst that begins to be expressed as early as E10.5 (Puelles et al., 2016).

In both (A,B), gradients indicate approximate onset and end of Tf expression. Cell shapes on the left of (A,B) indicate the cell types in which Tfs exert their function. A, from top to bottom: Dorsal radial glia progenitor cells, intermediate progenitor cells, migrating neuroblasts and mature neurons. B, from top to bottom: ventral radial glia progenitor cells, intermediate progenitor cells, migrating neuroblasts and early interneurons.

The majority of cortical GABAergic interneurons are generated in the MGE (Fig. 1C), which gives rise to cardinal types of interneurons expressing parvalbumin (PV) and somatostatin (SST). The CGE generates two other cardinal types of interneurons (Fig. 1C), one expressing vasoactive intestinal polypeptide (VIP) and another lysosome-associated membrane protein 5 (Lamp5) or inhibitor of DNA binding (Id2). Each of the four cardinal types of GABAergic interneurons is further subdivided into multiple subtypes based on their transcriptomic, morphological, and electrophysiological identities (Fig. 3A-E) (Gouwens et al., 2020; Pfisterer et al., 2020; Scala et al., 2020; Yuste et al., 2020). Cortical GABAergic interneurons in mice are produced from middle to late gestational stages (E9.5-E18.5), with MGE interneurons generated preferentially in the early period before E14.5 and CGE interneurons generated largely from E12.5 onwards (Miyoshi et al., 2007; Miyoshi and Fishell, 2011). Generation of GABAergic interneurons is controlled by a set of transcription factors (Fig. 4B). Thus, differentiation of PV and SST interneurons is regulated by the transcription factors Nkx2.1 and Lhx6 (Butt et al., 2005; Lavdas et al., 1999; Liodis et al., 2007; Susse et al., 1999), whereas VIP and Lamp5/Id2 subtypes are specified by the factors COUP-TFII, Adarb2, and Prox1 (Rudy et al., 2011; Vucurovic et al., 2010). More recent studies in lineage mapping (Mayer et al., 2018) and single-cell transcriptomics (Mayer et al., 2018; Mi et al., 2018) suggest that the terminal differentiation of cortical interneurons takes place largely postmitotically. Furthermore, it has been proposed that cortical interneuron subtype identity is determined through interaction with the environment (reviewed in Wamsley and Fishell, 2017). Indeed, a number of studies show how the environment controls generation and differentiation of GABAergic interneurons. For instance, BMP4 derived from meninges modulates the differentiation of PV and SST interneurons (Mukhopadhyay et al., 2009) and further control of interneuron differentiation is driven by Shh derived from the floor plate (Guasci and Lillien, 2003). A substantial role for activity-dependent maturation of interneuron subtypes has also been proposed. This is supported by whisker removal experiments which, e.g., impair maturation of PV and Reelin+/SST- neurogliaform interneurons (De Marco García et al., 2015; Jiao et al., 2006). Additionally, afferents from various neurons as well as interactions with glial cells have also been described to shape interneuron subtype identity (Denaxa et al., 2018; Luhmann et al., 2016; Thion et al., 2018; Tomassy et al., 2014).

Finally, neuronal diversity greatly varies between cortical regions, which is particularly true for principal neurons. For instance, some cortical regions (e.g., motor) lack or have a rudimentary layer 4, whereas others (e.g., visual V1) have an extremely complex layer 4 (Bernard et al., 2012; Yamawaki et al., 2014). Furthermore, the difference in gene expression between principal neurons in different cortical regions might be so large that even though they reside in the same layers, they are classified as separate transcriptomic subtypes based on the cortical area (Tasic et al., 2018).

Overall, owing to the remarkably diversity of neuronal features, recent efforts have attempted to draw correlations between subtypes by looking at morphology, electrophysiology, and gene expression (Gouwens et al., 2020; Scala et al., 2020) in order to arrive at a classification that describes cortical neurons from multiple modalities (Yuste et al., 2020).

3. Maternal-derived insults affecting fetal brain development

While a normal maternal environment is necessary for cortical circuits to develop correctly, a number of maternal insults can change the maternal environment and perturb cortical development of the fetus (Fig. 5). Sections 3.1–3.6 summarize our current knowledge of the major types of maternal-derived insults, focusing primarily on defining the insult and on how the insult arises in the mother, how it reaches the fetus, and how it affects the developing cortex, if known. The questions “what cell types in the developing cortex are affected by maternal insults?” and “why are those cell types affected?” are discussed in Section 4, where the concept of selective vulnerability to maternal-derived insults is introduced. The list of discussed insults is not exhaustive, and there are several other insults that are not included in the section, e.g., maternal depression, autoimmune disorders, and hypoxia, which have also been proposed to increase risk for neurodevelopmental abnormalities in the offspring.

Finally, and before proceeding with a discussion of maternal insults, it is important to be reminded that all maternal-derived insults have to pass several major barriers before they reach the fetal brain (Gude et al., 2020; Saunders et al., 2012), the placenta and blood-brain barrier being the major ones (Fig. 5). Both of these barriers protect the fetal brain from adverse environmental effects. The placenta is organized so as to support...
Fig. 5. Major types of maternal-derived insults that impair fetal brain development and lead to neurodevelopmental disorders. Schematic representation of maternal-derived insults that are known to impair fetal brain development at distinct stages. The insults are grouped into 5 major categories: maternal immune response to infections, direct fetal brain infections that are passed from mother to fetus via the placenta, maternal exposure to toxic substances such as alcohol, nicotine and others, maternal nutrient deficiency or overnutrition, and maternal stress. Note in the insets two major barriers that protect the fetal brain from maternal-derived insults – the placenta (SYN – syncytiotrophoblast, CTB - cytotrophoblast) that provides for exchange between maternal and fetal compartments while protecting fetal compartment from adverse factors, such as infections, toxic substances etc; and the blood-brain barrier that provides further level of protection between fetal blood and fetal brain.
the fetus with nutrients from maternal blood, while also providing a barrier against pathogens and other harmful factors (Gude et al., 2004; Pereira, 2018). The blood-brain barrier consists of endothelial cells and is further supported by astrocytes and pericytes to protect the fetal brain from harmful factors. Functional blood-brain barrier is formed early during brain development (second half of the first trimester), which is indicated by the distribution of tight junction proteins that are associated with the blood-brain barrier (Gude et al., 2004). However, it is not known how the structure and function of the blood-brain barrier change during development. While there is a solid evidence for a functional blood-brain barrier during fetal brain development (Saunders et al., 2014), as support cells - astrocytes and pericytes - are born after the brain vasculature is formed (Goadsby et al., 2017), it is likely that the structure of the fetal blood-brain barrier is different from the adult state, which might render it more sensitive to the maternal-derived insults. Importantly, each of the barriers, when compromised, could further contribute to the pathology of maternal-derived insults. Thus, disruptions in pathways necessary for forming a properly functional placenta or blood-brain barrier (for instance, due to genetic mutations) cause abnormalities in brain development and brain disorders in the adult offspring (Ben-Zvi et al., 2014; Woods et al., 2018).

3.1. Direct fetal brain infections

First reports that viral and bacterial infections in the mother could increase the risk of developing a psychiatric disorder for the offspring are dated to the beginning of the 20th century and were followed up by the hypothesis that schizophrenia could be caused by an infectious agent (Menninger, 1928). Later on, the association between maternal infections by viruses and bacteria and neurodevelopmental disorders in the offspring was established in epidemiological studies for a number of infectious agents, such as influenza (Mednick et al., 1988), rubella (Brown et al., 2001), cytomegalovirus (CMV) (Cheeran et al., 2009), Zika virus (ZIKV) (Mlakar et al., 2016), and others. Two mechanisms have been proposed for how viral/bacterial infection could affect fetal brain development – a direct mechanism, i.e., congenital infections that spread from mother to fetus, and an indirect mechanism that is mainly associated with the maternal immune response to infections. While for congenital infections it is often difficult to separate direct effects from indirect effects (since the mother will usually also have an immune response to viruses/bacteria that cause congenital infections), there are a number of infectious agents, such as influenza, that are very rarely transferred from mother to child and thus will have only an indirect effect on fetal brain development. In this section, we will focus on direct fetal brain infections (Fig. 5), whereas indirect immune response-related effects will be discussed in the following Section 3.2.

Although the association of congenital infections with a risk of abnormal cortical development was established for infectious agents such as CMV and rubella long ago and confirmed in multiple studies, e.g., (Perlman and Argyle, 1992), the mechanism underlying abnormal fetal development is still largely unknown. Most likely both viruses spread to the fetus via maternal blood and then infect the placenta. It has been shown that CMV from maternal blood could infect cells residing in placenta membranes, where it could also replicate and affect gene expression and cell differentiation (reviewed in Pereira, 2018). CMV infects the fetus via epithelial cells, and once in the fetus, CMV could infect virtually any brain cell type (Cheeran et al., 2009). CMV was proposed to exhibit teratogenic effects inducing chromosomal aberrations due to cell cycle arrest (Fortunato et al., 2000). In the developing brain, CMV protein machinery modulates the cell cycle and apoptosis of precursor cells (Cheeran et al., 2009), inhibits neuronal differentiation (Odeberg et al., 2006), and perturbs neuroblast migration (Shimura et al., 1997), which could underlie CMV-related cognitive abnormalities.

More is known for the effect of maternal ZIKV infections that cause microcephaly and cortical malformations in the offspring (Mlakar et al., 2016; Petribu et al., 2018). ZIKV can spread via placenta to fetus (Miner et al., 2016) due to its ability to infect fetal endothelial cells via AXL receptor tyrosine kinase (Richard et al., 2017). In the fetal cortex, ZIKV infects proliferating precursor cells around the ventricles, thus leading to cell cycle arrest, prevention of precursor differentiation, and ultimately apoptosis (Retallack et al., 2016; Zhang et al., 2016). Both neuronal and glial precursors can be infected by ZIKV (Li et al., 2018; Retallack et al., 2016).

3.2. Maternal immune response due to viral and bacterial infections

Maternal inflammation covers a larger spectrum of inflammatory reactions due to infections by bacteria, virus, protozoa, etc., and exposes the developing fetus to maternally secreted cytokines (Fig. 5). The association between viral and bacterial infections that do not cause/have very low incidence of congenital infections and increase risk for neurodevelopmental disorders was established in epidemiological studies for influenza (Mednick et al., 1988) or for various types of bacterial infections (Sørensen et al., 2009). Maternal immune response was proposed to be the main trigger of neurodevelopmental disturbances in the offspring. Both viral and bacterial infections induce the innate immune response via activation of Toll-like receptors (TLRs) on macrophages (Takeda et al., 2005; Akira, 2006), which leads to an increased release of proinflammatory cytokines in the maternal blood. It was hypothesized that maternal cytokines cross the placenta and spread into the developing fetus, including the fetal brain, where they could have either direct or indirect effects on precursor cells, immature neurons, and glia (Dammann and Leviton, 1997; Gilmore and Jarskog, 1997).

While mechanistic studies are difficult to perform in humans, maternal inflammation models have been established in rodents and in nonhuman primates. Early work in rodents was conducted using infectious strains of influenza that showed disruption in cortical development and schizophrenia-like behavior in the offspring as a result of maternal infections (Fatemi et al., 1999; Shi et al., 2003). However, since experiments with real pathogens require high levels of biosecurity, simpler models have been established. The two most common models include injections of polyinosinic-polycytidylic acid (poly I:C), which mimics viral double-stranded RNA and triggers a virus-induced immune response (Meyer et al., 2005; Zuckerman et al., 2003), and lipopolysaccharide (LPS), which is a bacterial cell wall endotoxin that triggers a bacteria-induced immune response. Implementation of these models revolutionized our understanding of how the maternal immune response is triggered and could impair fetal brain development. Both models accurately reproduce the actual innate immune response by a virus or bacteria: poly I:C triggers activation of TLR3, which specifically recognizes double-stranded viral RNA, and LPS activates TLR4, which recognizes bacterial cell wall (Kentner et al., 2019). It has been shown that maternal inflammation triggers an acute inflammatory response by activating proinflammatory cytokines, including IL-6, IL-8, IL-1β, IL-17a, and TNFα (Choi et al., 2016; Meyer, 2013). Such a proinflammatory profile resembles human epidemiological studies showing an association of the higher risk of developing a cognitive impairment/ neurodevelopmental disorder with an increase in IL-6, IL-8, and TNFα in maternal blood (Brown et al., 2004; Buka et al., 2001; Ghassabian et al., 2018; Goldstein et al., 2014).

Cytokines can affect development of the fetal brain by several means, of which the most recognized are via microglia as a mediator or by direct interaction with cytokine receptors on precursors and immature neurons. Although initially microglia activation in the fetal brain was naturally proposed to be a mediator of a maternal inflammation effect on fetal brain development (Pratt et al., 2013), some studies in a poly I:C model showed a lack of microglial activation (Giovanni et al., 2016; Snodders et al., 2015). In addition, an absence of microglia-activation gene expression signature was reported in a recent single-cell transcriptomics study of poly I:C (Kalish et al., 2021). Nevertheless, maternal poly I:C was found to alter microglia transcriptome and phagocytic function in the adult offspring (Mattei et al., 2017), which could indicate
that microglia mediate maternal inflammation effects later during postnatal life.

On the other hand, several studies supported a direct effect of proinflammatory cytokines on fetal brain development. Thus, a dramatic direct effect was shown for IL-6, which was able to expand cortical neuronal progenitors (Gallagher et al., 2013) and modulate neural stem cell renewal (Storer et al., 2018) in the fetal brain, which, in turn, could lead to behavioral deficits in the offspring (Smith et al., 2007). However, studies that analyze distribution of cytokine receptors across different cell types during cortical development are lacking, and unbiased analysis of cytokine receptor distribution in single-cell data could help to predict sensitivity of cortical cell types to maternal inflammation during corticogenesis.

While multiple studies have investigated the consequences of maternal inflammation in adult offspring, only limited data are available on how maternal inflammation affects fetal brain development. It has been shown that maternal inflammation modulates proliferation of neuronal precursors and migration of immature neurons (Stolp et al., 2011; Vasistha et al., 2020), which could cause abnormal development of cortical circuits that are characterized by impaired cortical laminauration, malformations, and redistribution of inhibitory receptors (Choi et al., 2016; Stolp et al., 2011; Vasistha et al., 2020). Most transcriptomic changes included immune response and hypoxia genes and genes involved in precursor proliferation (Canales et al., 2020). A single-cell transcriptionomics study of poly I:C effect on cortical development showed strong inhibition of protein translation in embryonic cortex, which leads to global alterations in protein composition in the cortex of the offspring affected by maternal inflammation and changes offspring behavior (Kalish et al., 2021). Naturally, such developmental disturbances are associated with marked behavioral deficits, such as decreased prepulse inhibition, altered social interaction, and decline in memory and cognition (Meyer et al., 2008, 2006; Richetto et al., 2014; Vasistha et al., 2020).

Importantly, several recent human studies confirmed the association between maternal inflammation and changes in functional connectivity in the cortex and cognition in the affected offspring (Rasmussen et al., 2019; Rudolph et al., 2018; Spann et al., 2018).

Lastly, it should be noted that, although the major focus in maternal inflammation research has been influenza-like infection, any viral/bacterial infection leading to acute or chronic inflammation could perturb fetal cortex development, including effects shown in poly I:C and LPS models. Furthermore, infectious agents that cause congenital infections, e.g., CMV, might have dual effects – due to direct fetal infection and the maternal immune response (Cheenan et al., 2009).

3.3. Maternal stress

Various types of stressful events during pregnancy have been associated with an elevated risk for the offspring to develop a neuropsychiatric disorder, such as schizophrenia (Khashan et al., 2008; Malaspina et al., 2008). Interestingly, it has been proposed that the immune response modulated by hormones (mainly glucocorticoids) in pregnant women during stress is the trigger for neurodevelopmental disturbances in the fetus (Fig. 5), thus resembling the effect of maternal infections on fetal brain development (Hantsoo et al., 2019). However, the etiology of the modulated immune response (hormone activation vs infections) and thus the pattern of cytokine activation in maternal stress differs from that in maternal infections. Furthermore, different types of stressors, such as acute, brief naturalistic, and chronic, differentially impact the activation/inhibition of the innate and adaptive immune systems (Segestrom and Miller, 2004). While immune profiles for different maternal stressors have been well studied and reviewed (Hantsoo et al., 2019), the mechanisms underlying differences in the immune response that translate into impact on fetal brain development are still unclear. Only a few recent epidemiological studies found an association between maternal stress-related changes in immune response and neurodevelopmental abnormalities in the offspring, e.g., stress-related lower concentrations of IL-8 correlated with neurological symptoms in neonates (Ghasabian et al., 2018), and higher levels of C-reactive protein were correlated with ADHD in boys (Shao et al., 2020). Additionally, stress modulates a number of neuroendocrine factors that include not only glucocorticoids, but also neuropeptides, growth hormones, insulin, and prolactin (Bronson and Bale, 2014; Webster Marketon and Glaser, 2008), and each of these could have a substantial impact on fetal brain development. Thus, it is likely that both immune and neuroendocrine factors underlie a plethora of molecular, cellular, and functional impairments due to stress during fetal brain development.

It has been hypothesized that the placenta plays a major role in mediating maternal stress response in the offspring (Bronson and Bale, 2016). Thus, stress factors reach the fetus by compromising the transplacental barrier, increasing its permeability to hormones, cytokines, and other potential mediators of developmental impairments. Furthermore, maternal stress hormones could further impair endocrine function on the placenta itself, impacting nutrient transport and placental growth. Once in the fetal compartment, a number of stress factors could have a great and variable impact. Thus, stress-associated glucocorticoids could dramatically affect fetal growth and lead to hyperactivity of the hypothalamic–pituitary–adrenal (HPA) axis and anxiety in postnatal life (Seckl and Holmes, 2007). At the cortical compartment, elevated glucocorticoids exhibit antiproliferative effects on cortical neuronal precursors by activating glucocorticoid receptors that translocate in the nucleus and perturb transcription of genes involved in proliferation (Carson et al., 2016). Such inhibition of precursor proliferation could reduce the number of cortical neurons produced and have dramatic effects on the assembly of cortical circuits because there are fewer neurons and their density is decreased. Among other major stress factors, cytokines were proposed to have an important role by inducing further inflammation in the placenta and potentially cause a direct effect on cortical development, as described in Section 3.2.

Maternal stress-derived factors also affect migration (Bittle et al., 2019) and postnatal maturation of cortical neurons (Lussier and Stevens, 2016; Murmu et al., 2006; Wang et al., 2018), although how these disturbances arise is unknown. The effect of maternal stress on cortical maturation leads to miswiring and disruption of cortical circuits in mouse models. Importantly, studies in humans confirmed that maternal-derived stress alters development of functional cortical connectivity (Scheinost et al., 2017), including the frontolimbic pathway (Lautarescu et al., 2020).

3.4. Maternal malnutrition

The impact of maternal nutrition on fetal brain development cannot be overestimated. Considerable data show that both under- and overnutrition might influence fetal brain development and contribute to neurodevelopmental disorders (Fig. 5). One of the more drastic effects comes from severe maternal undernutrition during famine, which increases the risk of schizophrenia, psychoses, depression, and other psychiatric disorders (Roseboom et al., 2011). Similarly, maternal overnutrition such as obesity correlates with a higher incidence of psychiatric disorders in the offspring (Buss et al., 2012; Moody et al., 2017). Finally, a certain range of many essential nutrients is necessary for normal fetal brain development and concentrations above or below normal range could both have a detrimental effect on the fetal brain. For instance, too high maternal levels of vitamin A are associated with microcephaly and other brain malformations in the offspring (Rothman et al., 1995), whereas maternal deficiency in vitamin A contributes to psychiatric disorders, such as schizophrenia (Bao et al., 2012). Likewise, both maternal deficiency and excess of folic acid lead to impaired cortical architecture in the offspring and abnormal behavior in animal models (Harlan De Crescenzo et al., 2020).

Nutrients are transferred from mother to embryo via the placenta where, in simplified terms, they are used as building blocks and energy
for developing embryonic tissues. Thus, a lack of nutrients would mean fewer building blocks and less energy, which is why growth restriction constitutes the most common complication of undernutrition. In the embryonic cortex, it translates into a reduction in precursor proliferation due to the lower rate of mitosis (Gould et al., 2018), which, depending on the severity, could lead either to general microcephaly or cortical thinning. Undernutrition also retards differentiation, which could delay maturation of cortical circuits and in turn induce behavioral impairments in learning and memory (Gould et al., 2018). Additionally, during a normal neuronal differentiation process, a cell transits from glial-fate radial glial cell to neural-fate precursor and then immature neuroblast, which has high energy demands due to extensive changes in gene expression and morphogenesis. Thus, energy deficiency impairs neuronal differentiation, which could cause apoptosis (Cabello-Rivera et al., 2019). Finally, neuronal migration and maturation are also cellular processes that demand energy. If energy is lacking, neurons are misplaced and cortical circuits are miswired, and, as a result, mental abnormalities develop in the offspring (Antonow-Schlorke et al., 2011; Sanz-Morello et al., 2020).

Studies investigating the effects of overnutrition on fetal brain development have usually focused on obesity (Fig. 5). Extensive work in animal models showed that maternal high-fat diet and obesity impact fetal brain development via several routes, the most prominent being chronic inflammation and hormonal regulation (Moody et al., 2017). While propagation of maternal inflammatory and hormonal signals to the fetus and their impact on cortical development has been discussed above in Section 3.2, one of the most important obesity-related hormones, leptin, requires special attention here. Leptin is transported from mother to fetal brain where it binds to widespread expressing receptors and promotes overall brain development. In the cortex, leptin modulates proliferation of precursor cells (Udagawa et al., 2006a). Caloric restriction lowers concentrations of leptin in maternal blood and fetus (Moody et al., 2017) and increases apoptosis of precursor cells in the developing cortex (Udagawa et al., 2006b). In addition, it was proposed that high levels of leptin stimulate neuronal differentiation, whereas low levels support an undifferentiated precursor state (Udagawa et al., 2005). In addition, leptin may also promote differentiation of glial precursors towards oligodendrocyte cell fate (Udagawa et al., 2007). It is likely that leptin affects cell differentiation by modulating cell fate transcription factor expression, such as Hes1 (Udagawa et al., 2007), although the mechanisms underlying the potentially direct effect of leptin on precursor cells have not been explored.

Finally, fetal brain development depends on a number of specific maternal nutrients, and several of them have been studied in the context of cortical development. Examples include salt overconsumption, which changes spine density and morphology in the limbic cortices (Dingess et al., 2018); iron deficiency, which reduces neuronal metabolism in the cingulate cortex (DeUngria et al., 2000); and low levels of folic acid, which lead to thinning of the cortical regions and are associated with psychosis (Eryilmaz et al., 2018).

3.5. Drug abuse, smoking, alcohol, medications, and other toxic substances

Multiple toxic substances that are unnatural for mother-fetus interaction could potentially damage fetal cortex development (Fig. 5). These include not only pollutants, such as heavy metals, particulate matter, and pesticides, but also substances derived from smoking, alcohol consumption, medications, and drug abuse. Although the placenta and fetal blood-brain barrier do provide two levels of defense against toxic chemical penetration, it has been shown that many substances are able to penetrate the placenta and large molecules could reach the fetal compartment, albeit at a slower rate. Furthermore, a fully functional blood-brain barrier requires support cells such as astrocytes and pericytes, which have not yet been born during early development when the fetal vasculature is established (Goasdoué et al., 2017). Thus, the most common route for toxic substances to reach the fetal brain is via maternal blood and placenta.

One of the first pollutants to be associated with an increased risk of abnormal brain development was methylmercury, which enters the human body by consuming contaminated seafood. Maternal exposure to methylmercury impairs fetal brain development, the most common effects being microcephaly, decreased number of cells, disturbed neuronal migration, and gliosis (Choi, 1989). Fetal cortex is in particular affected due to interference with cell cycle and inhibition of precursor proliferation, leading to cortical thinning and abnormal cytoarchitecture that could cause cognitive dysfunction and mental retardation in the offspring (Choi, 1989; Faustman et al., 2002). A similar behavioral phenotype has been reported for maternal exposure to other heavy metals, e.g., lead (Opler and Susser, 2005). Exposure to heavy metals could modulate the expression of key hormone receptors and growth factors, such as glucocorticoid receptor and brain-derived neurotrophic factor (BDNF), which in turn affect animal behavior, and such a phenotype is epigenetically transmitted for several generations (Sobolewski et al., 2020).

Air pollution by particulate matter is a common problem in urban areas and has been associated with a risk of abnormal cognitive development, autism, and mental retardation (von Ehrenstein et al., 2014; Wang et al., 2017). It has been shown that maternal nanoparticles reach fetal tissues and could be detected in various brain regions, including the cortex (Takeda et al., 2009). Although the mechanisms underlying how maternal particulate matter affects cortical development are not clear, it has been shown that maternally derived particles (introduced by inhalation) activate glial cells and reduce the number of inhibitory neurons in the cortex (Umezawa et al., 2018).

Maternal smoking and alcohol drinking correlate strongly with a risk of cognitive impairment in the offspring (Ekbлад et al., 2015; Riley et al., 2011). For smoking, associated nicotine and toxins have been shown to cross the placenta and reach various fetal tissues. Nicotinic acetylcholine receptors (nAChRs) play an important role in brain development. Maternal-derived acetylcholine desensitizes fetal nAChRs, leading to loss of function of nAChR (Cohen et al., 2005). The block of nAChR could affect inhibitory GABAergic synapses in the prefrontal cortex and produce excitation-inhibition imbalance (Flores-Barrera et al., 2017), which could be associated with abnormalities in cortical maturation that have been reported in children affected by maternal smoking.

Exposure of the fetus to an excess of alcohol results in multiple, often severe abnormalities in brain development, collectively referred to as fetal alcohol spectrum disorders (FASD) (Riley et al., 2011). Alcohol easily crosses the placenta and affects a variety of developmental processes in the fetal cortex. The reported effects of FASD are widespread, such as hampering cell differentiation signaling (Deltour et al., 1996) and inducing metabolic impairments (Miller and Dow-Edwards, 1988; Snyder and Singh, 1989) and oxidative stress (De La Monte and Wands, 2001; Henderson, 1999). In cortical neurons, these pathways trigger cell death and thus decrease the number of surviving neurons (reviewed in Pfister and Khodosevich, 2017). Additional effects include disruption of cortical progenitor proliferation and neuronal migration (Miller, 1993, 1992).

Maternal drug abuse might also exert an effect on fetal brain development. Drugs such as marijuana, cocaine, and opiates cross the placental barrier and could reach the fetal brain. However, although some studies support a correlation between maternal drug abuse and brain dysfunction in their offspring (Campolongo et al., 2007), mechanistic studies for cortical effects are lacking for most abusive drugs or were performed in cell cultures. Mechanistic studies of drug effects on corticogenesis have been conducted for cannabinoids, where maternally derived exogenous cannabinoids likely interact with the endogenous cannabinoid system of mother and fetus, and such interplay could modulate migration and maturation of cortical neurons (Berghuis et al., 2005).

Finally, fetal cortex might be more vulnerable to medications, which
are less harmful in adulthood. One striking example is valproate, which was reported to be associated with neurodevelopmental disorders in the offspring after prenatal exposure (Christensen et al., 2013). Recently, it was shown that valproate reduced neuronal differentiation and impaired layer formation in human cortical organoids (Cui et al., 2020). At the gene expression level, a number of pathways associated with synapse formation and function were perturbed by valproate exposure. These data confirm that valproate has a profound impact on early human cortex development. Importantly, maternal use of even common medicines, such as paracetamol, could affect fetal cortical development due to the increase in cytokine release into the fetal blood, which derives from the inflammatory response of the placenta to the medicine (Koehn et al., 2020). Such a proinflammatory response further impacts gene expression in the fetal brain, with >1000 genes being up-/down-regulated (Koehn et al., 2020).

### 3.6. Interaction of insults

Maternal-derived insults interact extensively and the overall effect of the maternal environment on fetal cortex development is a result of the combinatorial impact of these insults. The initial effects might also alter and nonoverlapping, for example, when a pair of insults affect different developmental processes or cell types in the cortex. However, early developmental impact often has consequences for later development and adult cortical function (Vasistha et al., 2020), and the cortex is characterized by high interconnectivity of functional cortical regions, which mutually affect each other’s function (Shipp, 2007). Thus, the ultimate effect of maternal insults should converge on common circuits, where in most cases insult interaction exacerbates the overall effect on brain development (Buuse et al., 2003; Khambkadone et al., 2020); however, one insult might also inhibit some effects of another insult.

The interaction of environmental insults has only recently received more attention and some combinations of interacting insults have been studied that confirm a complex interplay and the convergence of maternal insult-derived effects, e.g., maternal inflammation and stress (Giovanoli et al., 2013; Monte et al., 2017), toxic substances and stress (Sobolewski et al., 2020), and nutrition and ZIKV infection (Barbeito-Andrés et al., 2020; Gilbert-Jaramillo et al., 2019). Importantly, these studies show that interaction of the insults is complex and goes far beyond a simple summary of the effects. Furthermore, when one insult precedes another, the first insult might increase vulnerability to the second insult, which was shown for maternal inflammation-1st and stress-2nd (Giovanoli et al., 2013; Monte et al., 2017) and malnutrition-1st and congenital ZIKV infection-2nd (Barbeito-Andrés et al., 2020). Importantly, it is likely that the plethora of initial effects for such a combinatorial impact of maternal environment converges on the most sensitive and vulnerable cortical cell types and circuits. The concept of how selective vulnerability of neural cells to maternal-derived insults could underlie cognitive phenotype is introduced in the next section.

### 4. Selective vulnerability of cortical neurons to maternal-derived insults

#### 4.1. The concept: selective vulnerability is encoded by time, position, and transcriptome

As discussed above in Section 3, maternal-derived insults could severely impact the development and maturation of the cortex. However, recent studies, particularly single-cell analyses, demonstrated that the cortex consists of a multitude of neuronal subtypes and these subtypes also have distinct developmental profiles. This raises obvious questions: how and when do maternal-derived insults affect each cortical neuron subtype during development? Furthermore, if certain subtypes are affected more than others, why?

Our knowledge of the complexity of the cortex has evolved dramatically over the last decade as a result of technological breakthroughs. Thus, most recent studies capturing transcriptomic, morphological, and electrophysiological signatures from thousands of cortical neurons in the mature cortex (Gouwens et al., 2020, 2019; Scala et al., 2020) reveal an enormous diversification of each of these parameters, with transcriptome being most diverse. Such complexity is established during development and the programs for specifying individual subtypes of cortical neurons are now emerging (Bella et al., 2020; Mayer et al., 2018; Nowakowski et al., 2017; Telley et al., 2019). Therefore, studies of cell type-specific changes in gene expression during development and maturation provide the temporal information required to assess changing vulnerabilities to maternal-derived insults. In order to comprehend the impact of various maternal-derived insults on cortical functions, it is important to understand the origin of such selective vulnerability. We propose that cellular vulnerability to maternal-derived insults changes with time, positional identity, and transcriptional signature, and that these three factors might also influence each other (Fig. 6A-D). As described in Section 3, each insult is transmitted from mother to developing embryonic cortex via a set of routes and factors. Thus, for any insult to directly affect a developing cortical neuron, there should be a “receiving set” in the affected neuron, and without such a receiving set, the insult will not have a direct influence on the neuron (Fig. 6A). The receiving sets are molecules that could directly interact with maternal factors: in maternal inflammation, for example, these could be IL receptors. Alternatively, receiving set molecules might intracellularly propagate signaling of maternal factors: in maternal inflammation, these could be the kinases that respond to IL signaling. Those types of neurons and their progenitors that have the best-fitting receiving sets for a particular insult at the developmental timepoint when the insult reaches the embryonic cortex will mount the largest direct response to the insult. It is important to note that after a direct response there might be additional, even more complex indirect effects on other neuron types. However, the initial direct effect of an insult will determine all indirect effects and should depend on the availability of receiving sets in the developing neurons. Such receiving sets will be encoded by genes, and by revealing gene expression in each neuron type during the time when the insult is transmitted from mother to embryo, we should be able to understand whether and why specific neuron types are more vulnerable than others.

Recently, a number of studies in the mature cortex have described an effect of a maternal insult on certain layers of cortical principal neurons or cardinal types of GABAergic interneurons. In particular, several single-cell omics studies of mature cortex have shown that, transcriptomically, only some neuronal subtypes seem to be affected in brain disorders, whereas other subtypes are largely unchanged (Batiuk et al., 2020; Mathys et al., 2019; Pfisterer et al., 2020; Schirmer et al., 2019; Velmeshev et al., 2019), and the variability of gene expression changes due to a brain disease between subtypes of human cortical neurons is enormous, e.g., from <50 to >1000 differentially expressed genes per neuronal subtype for epilepsy (Pfisterer et al., 2020). Additionally, single-cell analyses in gene knockout studies have begun to validate on a functional level those factors that could be a part of receiving sets in the affected neuronal types, such as Grin1 expression in MGE-derived GABAergic interneurons (Makadeyan et al., 2020). While single-cell investigations addressing the impact of maternal insults on cortical development are still lacking, several recent studies using transgenic animals and neuronal type-specific expression markers have uncovered the effects of maternal insults on cortical neuronal types. For instance, it has been shown that maternal inflammation differentially impacts MGE and CGE progenitors, which depends on the time of immune activation (Vasistha et al., 2020). As a result, early maternal inflammation led to the reduction of PV- and SST- interneurons but not GABA-derived subtypes such as CR+/-/SST- and VIP+. Likewise, prenatal infection with West Nile virus (WNV) impacts neurons but not neural precursors (Brault et al., 2016; Desole et al., 2019).
Fig. 6. Selective vulnerability of cortical cell types to maternal-derived insults.

A) Concept of selective vulnerability to maternal-derived insults that is based on expression of receiving sets. Any insult to directly affect a developing cortical neuron should have a receiving set in the affected neuron, and without such a receiving set, the insult will not have a direct influence on the neuron. Receiving sets are transmembrane and intracellular components that mediate neuronal response to an insult. Example in the panel shows that Insult A has a receiving set in the left green cell, but not in the right green cell, and the situation is opposite for Insult B. Thus, the left green cell will respond to Insult A, but not Insult B, and vice versa for right green cell. Importantly, gene expression in the right green cell could change, e.g. as a result of developmental program or cell state activation, and the changed cell (now in blue) could express receiving set A, thus being vulnerable to Insult A.

B) Selective vulnerability depends on developmental time. The left panel shows vulnerability plot for a cell during development that is based on expression of Gene A, a major component of receiving set for Insult A. Certain amount of Gene A expression product in a neuron is necessary to mediate the effect of Insult A (indicated by the threshold line). Insult A occurring outside of the vulnerable window do not have an effect on the neuron, whereas Insult A occurring later during development will be “received” by Gene A product and trigger direct insult-related response. Thus, based on the expression of Gene A, a cell type can be predicted to be affected or unaffected, orange and green cells in the right panel, respectively.

C) Selective vulnerability depends on type of insult. Left panel shows vulnerability plot for a cell during development that is based on expression of Gene A, a major component of receiving set for Insult A, and Gene B, a major component of receiving set for Insult B. Thus, when both Insult A and B impact the cell during early development, only Insult A could trigger a response in the cell, whereas during later development only Insult B could trigger a response. At a transcriptome-wide level (right panel), maternal-derived insults will modulate distinct intracellular changes and eventually differential cell states.

D) Selective vulnerability depends on the anatomical location of cell types. The upper panel shows that Insult A acts from the ventricle and impacts radial glia progenitor cells (red) that have apical process exposed to the ventricle surface, whereas intermediate progenitor cells and neuroblasts (blue) are not exposed to the insult. Instead, the bottom panel shows that Insult B acts from the surface of the developing cortex, thus impacting postmitotic neurons migrating superficially in the marginal zone (red, bottom panel) but not other cells.
4.2. Selective vulnerability of cortical neurons to different types of maternal insults

In the following sections, we will review the literature and provide evidence for selective vulnerability of cortical neuron subtypes to various maternal-derived insults. In addition, we will discuss how selective vulnerability of those subtypes that were shown to be affected could be translated into psychiatric/neurological phenotype of the offspring. Fig. 7 summarizes our knowledge for selective vulnerability in terms of developmental period and cellular processes (precursors proliferation, neuroblast migration, neuronal differentiation) for each type of maternal-derived insults.

4.2.1. Direct fetal brain infections

Most data for selective neuronal vulnerability in congenital infections are available for CMV and ZIKV, which show two distinct mechanisms for selective vulnerability. For CMV the viral tropism is very broad and the vulnerability is mediated largely by intracellular factors, but ZIKV has very specific tropism, infecting only particular types of progenitors.

Although some studies documented a differential impact of CMV infection on neuronal types, e.g., CMV-infected upper layer neurons being slower in reaching upper cortical layers (Shinmura et al., 1997), most studies suggest a broad tropism of CMV in the developing cortex, spanning precursors (Cheeran et al., 2005; McCarthy et al., 2000), migrating neuroblasts and immature neurons (Odeberg et al., 2006; Poland et al., 1990), as well as glial cells (Pulliam et al., 1995; Schut et al., 1994; Spiller et al., 1997). In neuronal progenitors and immature neurons, CMV reduces differentiation and increases apoptosis (Odeberg et al., 2006; Shinmura et al., 1997). Interestingly, despite the ability of CMV to infect multiple cell types, it has been noted that no detectable viral proteins are seen in neurons (Lokensgard et al., 1999; Pulliam et al., 1995).

Fig. 7. Periods of developmental vulnerability for maternal-derived insults. Schematic representation of the differential impact of maternal-derived insults on the fetal cortex over the course of development. For each type of insults, developmental timeline in gestational weeks (GW) is shown on one side, with the stages of proliferation (green dividing cells), migration (orange migrating cell) and maturation (red maturing cell) indicated on the opposite side. Gradients, colored by red, highlight a period of highest developmental vulnerability for each insult, which show some commonalities and differences. Thus, the early impact of maternal nutrition is contrasted by the late vulnerability stage of maternal stress. The highest vulnerability to maternal immune response and direct fetal brain infections occurs around similar time periods stretching from GW8 to GW24. The highest developmental vulnerability to the exposure to toxic substances has a bimodal mode and fall into late first trimester and third trimester.
et al., 1995). Instead, the majority of neuropathological changes are thought to be the result of an impact on astrocytes and endothelial cells in which viral gene expression has also been noted (Lokensgard et al., 1999; McCarthy et al., 1995; Poland et al., 1990). Thus, differential vulnerability was proposed to occur more at the level of viral replication and protein synthesis and not at entry, where gila-fate differentiation of the precursors would promote CMV production and neuronal fate would repress it (Cheeran et al., 2005).

In contrast to CMV, ZIKV shows specific tropism towards the RGCS in the developing fetal brain (Brault et al., 2016; Cugola et al., 2016; Dang et al., 2016; Garcez et al., 2016). As a result, progenitor divisions are severely affected, leading to cortical thinning and microcephaly. Developmentally, the risk of ZIKV-related neurodevelopmental abnormalities is greater during the first trimester than during the second and third trimester (Reynolds et al., 2017; Shaprio-Mendoza et al., 2017). This could be explained either by higher expression of entry receptors at RGCS or by the larger scale of proliferation reduction. Importantly, studies using human iPSC models of cortical development confirm selective vulnerability of RGCS, showing that, in contrast to neural progenitors, immature neurons are less susceptible to ZIKV infection (Tang et al., 2016). The selectivity of the tropism might be explained by the expression of the AXL receptor protein on neural precursors (Meerens et al., 2017; Nowakowski et al., 2016), which is thought to be an entry receptor for ZIKV. Surprisingly, a related Flaviviridae member, the West Nile virus (WNV), shows the opposite selective tropism and does not infect precursor cells but instead has been shown to impact neurons (Brault et al., 2016; Desole et al., 2019).

While these studies suggest differences in the initial effect of CMV and ZIKV on the developing brain, the neuropathological outcomes are shared, as both result in microcephaly and other neurodevelopmental disorders (Mlakar et al., 2016; Perlman and Argyle, 1992). However, differentiating the vulnerabilities of cell types requires a detailed transcriptomic understanding of viral response in neurons and their progenitors.

4.2.2. Maternal immune response due to viral and bacterial infections

Several cytokines, such as IL-6, IL-8, IL-17a, TNFa, and others, have been reported to mediate the direct effects of maternal inflammation on fetal brain development (Estes and McAllister, 2016; Oskvig et al., 2012; Smith et al., 2007). Of these, IL-6 and IL-17a have been demonstrated to mediate the major effects of maternal inflammation on cortical development and mouse behavior (Choi et al., 2016; Shin Yim et al., 2017; Smith et al., 2007). However, a detailed characterization of the effect of individual cytokine proteins on developing cortex or expression of their receptors in embryonic progenitors and neurons has not yet been carried out.

At the cellular level, maternal inflammation has been described to impact several cell types across developmental stages. The acute inflammatory response affects both dorsal and ventral cortical progenitors, which generate principal neurons and GABAergic interneurons, respectively (Baines et al., 2020; Ben-Reuven and Reiner, 2019; Le Belle et al., 2014; Stolp et al., 2011; Vasistha et al., 2020). While neural progenitors seem to be the primary targets, it is likely that the initial transcriptomic changes cascade into further impact on neurons that are derived from the affected progenitors. Thus, maternal inflammation has been shown to affect expression of migration-related genes (Smith et al., 2007) as well as the migration itself by modulating the direction and/or speed of interneuron neuroblasts (Vasistha et al., 2020). Furthermore, postnatal maturation of interneurons was also affected (Canetta et al., 2016; Vasistha et al., 2020).

Although an impact on glutamatergic principal neurons has been described (Choi et al., 2016; Shin Yim et al., 2017), excitatory synaptic inputs in the medial prefrontal cortex and hippocampus were found to be undisturbed (Ito et al., 2016; Patrich et al., 2016; Zhang and van Praag, 2015). In contrast, a large body of evidence points towards GABAergic inhibitory neurons (Meyer et al., 2008), and specifically PV+ interneurons, as being the most affected cell type (Jiang et al., 2013; Meyer et al., 2008; Ricchetto et al., 2013; Steullet et al., 2017; Thion et al., 2018; Vasistha et al., 2020). This is also reflected in physiological studies in which a reduced connectivity to principal neurons was found for PV+ but not CR- or SST- interneurons (Canetta et al., 2016). Nevertheless, selective vulnerability of another MGE-derived cardinal neuronal type, namely, SST+, was reported, and the most recent data show that the effect of maternal inflammation on SST+ interneurons might be even greater than on those expressing PV (Vasistha et al., 2020). Interestingly, SST+ GABAergic neurons play a key role in forming transient circuits that guide cortical maturation (Anastasiades et al., 2016; Marques-Smith et al., 2016), and a disturbance of these neurons could thus impair subsequent functional maturation of adult cortical circuits. Importantly, for maternal inflammation, it has been clearly confirmed that selective vulnerability of neuron types to maternal-derived insults depends on the time when the insult occurs. Thus, whereas progenitors for MGE-derived subtypes of GABAergic neurons are selectively vulnerable when maternal inflammation takes place at gestational day (GD) 9.5 in mice, CGE-derived types of GABAergic neurons are selectively vulnerable at GD12.5 (Vasistha et al., 2020). Moreover, at a later gestational period, GD17.5, both MGE- and CGE-derived progenitors are vulnerable.

Finally, the first unbiased analysis of the impact of maternal inflammation on cortical development using single-cell transcriptomics was recently published and showed sex- and cell type-specific effects of maternal inflammation (Kalish et al., 2021).

4.2.3. Maternal stress

Maternal stress reaches the developing embryo via a plethora of immune and neuroendocrine factors, which show a differential impact on the developing cortex, both in terms of time and subtype. Indeed, a higher risk of maternal stress-related neurodevelopmental disorder is associated with exposure to maternal stress during the second and third month of pregnancy, i.e., first trimester (Malaspina et al., 2008). Rodent models of maternal stress during early gestational stages (GD1-GD7) have shown an increase in placental cytokine signaling by upregulating IL-6, IL-1b, IL2RA, and PTGS2, leading to long-term behavioral changes such as an increase in locomotor activity (Bronson and Bale, 2014).

Although comprehensive studies for selective vulnerability of cortical neurons to maternal-derived stress are still lacking, interneuron progenitors in the MGE were demonstrated to be particularly affected by the insult (Uchida et al., 2014). Such selective vulnerability is likely underlined by specific expression of the glucocorticoid receptor in the MGE, but not in the dorsal progenitors that generate principal neurons (Uchida et al., 2014). Furthermore, MGE progenitors are more vulnerable to the glucocorticoid receptor agonist dexamethasone, and thus glucocorticoid receptor, encoded by Nr3c1 gene, might be a good example of a receiving set protein mediating the response to an insult. Additionally, interneuron neuroblasts show an impaired migration owing to the reduct dysfunction caused by prenatal maternal stress (Bittle et al., 2019; Stevens et al., 2013). Therefore, a marked selective loss of PV+ interneurons probably due to abnormal migration was observed in the mPFC and somatosensory cortex of juvenile mice exposed to prenatal stress (Lussier and Stevens, 2016; Uchida et al., 2014).

At a global level, morphometric analyses suggest a selective vulnerability of certain cortical regions to maternal-derived stress, where a decrease in gray matter in the prefrontal, premotor, and temporal cortices has been reported (Buss et al., 2016; Favaro et al., 2015).

4.2.4. Maternal malnutrition

While there are no human data (due to lack of studies) for vulnerability of cortical neurons to malnutrition, animal model-based reports demonstrate that vulnerability depends on the developmental time. Thus, the majority of data provide evidence for an impact of maternal malnutrition on early brain development, including the cortex (MRC
Protein deprivation in the maternal diet has a major effect on fetal brain development. The effects vary depending on the stages when the deprivation occurs, and it appears that an earlier gestational period, such as the first half, is the most vulnerable (Chertoff, 2015; Gressens et al., 1997). Maternal protein deprivation during both the preimplantation and gestational periods has been shown to impair neural precursor proliferation and differentiation capacities for interneurons and principal neurons (Gould et al., 2018). However, protein deprivation only during preimplantation resulted in altered neuron proportions in specific layers of the postnatal cerebral cortex, suggesting selective vulnerability of their precursors to early induced lack of proteins (Gould et al., 2018). Additionally, it seems that precursors of GABAergic neurons are more prone to apoptosis due to undernutrition (Gould et al., 2018).

In other instances of malnutrition, excess of maternal salt exposure resulted in differential vulnerability between infralimbic and prelimbic prefrontal cortices, which resulted in an aberrant reward-seeking behavior (Bingess et al., 2018).

4.2.5. Drug abuse, smoking, alcohol, medications, and other toxic substances

Although a number of studies have reported the association of toxic substance exposure with neurodevelopmental abnormalities, mechanistic knowledge is again very limited. Gestational exposure to alcohol as FASD is one of the few examples for which some mechanistic data are available, including selective vulnerability, likely due to availability of robust animal models. Vulnerability towards maternal-derived alcohol has been reported for several types of principal neurons and GABAergic interneurons. The impact on principal neurons was observed to be higher for layer 4–5 neurons (Olney et al., 2002), which could be due to the initial effect on their progenitors (Miller, 1996, 1992). For GABAergic interneurons, a specific vulnerability of PV+ cardinal type has been observed in the frontal cortex (Hamilton et al., 2017; Moore et al., 1998).

4.3. Common selective vulnerability to insults: most vulnerable neurons and most vulnerable time

As we have shown previously, there is abundant evidence for selective neuronal vulnerability to maternal-derived insults during cortical development, which raises further questions: do certain neurons or their progenitors exhibit a common vulnerability across all insults, which could be considered “most vulnerable neurons”? Furthermore, is there a developmental period when the cortex is most sensitive to maternal-derived insults, so-called “most vulnerable time”? At the moment, there are too few data to answer the first question. Even for the available data we should further consider whether the reported selective vulnerability for a certain insult is more a result of study design bias: more tools are available to study the more studied neurons and thus further investigations tend to continue being focused on the most studied neurons. A striking example for such a bias is PV+ interneurons since the vast majority of studies of how maternal-derived insults affect cortical GABAergic interneurons focus chiefly on PV+ interneurons, e.g., (Canetta et al., 2016; Meyer et al., 2008; Steullet et al., 2017; Uchida et al., 2014). Although this might give the impression that PV+ interneurons are by far most vulnerable to maternal-derived insults, more recent data show that SST+ interneurons might be even more greatly affected (Vasistha et al., 2020). Moreover, modulation of CGE progenitor proliferation by maternal-derived insults implies vulnerability of CGE-derived interneuron subtypes (Vasistha et al., 2019). Finally, large gene expression changes in non-PV interneurons have been demonstrated in single-cell transcriptomics studies of the mature prefrontal and temporal cortices of patients with autism spectrum disorder (Volm-Mehevet al., 2019) and epilepsy (Pésterer et al., 2020) - brain disorders that arise due to impairment in brain development, including maternal insults.

More data are available to answer the second question for “most vulnerable time”. A number of studies that are referenced above showed in a less biased fashion higher vulnerability of cortical neurons to most maternal-derived insults during early embryonic development, which when related to human gestational period could be the second half of the first trimester. This period is characterized by the peak of neurogenesis (Fig. 1F), and thus proliferation of neuronal progenitors might represent the developmental process most vulnerable to maternal-derived insults. Modulation of progenitor proliferation by an insult will change the number of generated neurons, which could lead to profound consequences in the mature brain, such as malformations and miswiring of neuronal circuits. However, it is important to note that a change in number or density for a certain neuronal type is one of the easiest insult-associated readouts. In addition, studies of neuronal maturation and connectivity usually take longer and require more effort, which could lead to a bias because fewer data are available for impairments in neuronal maturation and connectivity after maternal-derived insults. Nevertheless, it seems that the developmental period when most cortical neurons are generated, i.e., peak of proliferation, represents the most vulnerable time for maternal-derived insults.

5. Conclusions and future studies

Due to rapid technological advances, our understanding of how maternal-derived insults could affect fetal brain development and of the consequences of such insults in the mature brain has expanded dramatically in recent years. First of all, we have begun to realize that the complexity of neuronal cells in the brain is far larger than previously assumed. In particular, it now becomes obvious that the cortex is the most complex tissue not only in the brain, but in the whole body of mammals (Yuste et al., 2020). Furthermore, new animal models have been developed and established in the field that can reproduce maternal insults better than before. These models have already helped us to understand mechanistically how maternal insults are transferred to the fetal brain and how neurons and their progenitors are affected by the insults. Finally, increased accessibility of epidemiological data from large cohorts and the development of new computational methods have made it possible to perform a number of large-scale, high-power epidemiological studies to test associations between maternal-derived insults and brain disorders in the offspring. Nevertheless, to further our understanding of which neurons are most vulnerable to maternal-derived insults and when they are most vulnerable, future research should be focused on developing more models, on performing unbiased studies of insult impact on neuronal subtypes, and on translating results towards diagnostics and clinical applications. Currently, a systematic approach is lacking for cross-comparisons between different insults, leading to a large variability in the insult parameters that are modeled, such as gestational time when an insult is applied, dosage of an insult, and how an insult is applied (intraperitoneally, intravenously, subcutaneously, etc.). Thus, optimizing the parameters for modeling each insult and benchmarking across laboratories will help to create models that could be used to comprehensively compare studies. In addition, although studies focusing on certain neuronal subtypes are essential for understanding the mechanisms of maternal insult impact on those most vulnerable and/or important for cortical function neurons, initial, unbiased screens should be performed to determine how an insult affects all types of cortical neurons. As for now, single-cell analysis capturing gene expression changes in all cortical neuron subtypes upon maternal insult is potentially the most powerful approach for such unbiased screening. This unbiased approach would help us to avoid being side-tracked by ongoing trends in research or focusing on simple readouts of maternal insult effects.
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Appendix A. The Peer Review Overview and Supplementary data
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