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Review article

Multisensory cortical processing and dysfunction across the neuropsychiatric spectrum

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ABSTRACT

Sensory processing is affected in multiple neuropsychiatric disorders like schizophrenia and autism spectrum disorders. Genetic and environmental factors guide the formation and fine-tuning of brain circuitry necessary to receive, organize, and respond to sensory input in order to behave in a meaningful and consistent manner. During certain developmental stages the brain is sensitive to intrinsic and external factors. For example, disturbed expression levels of certain risk genes during critical neurodevelopmental periods may lead to exaggerated brain plasticity processes within the sensory circuits, and sensory stimulation immediately after birth contributes to fine-tuning of these circuits. Here, the neurodevelopmental trajectory of sensory circuit development will be described and related to some example risk gene mutations that are found in neuropsychiatric disorders. Subsequently, the flow of sensory information through these circuits and the relationship to synaptic plasticity will be described. Research focusing on the combined analyses of neural circuit development and functioning are necessary to expand our understanding of sensory processing and behavioral deficits that are relevant across the neuropsychiatric spectrum.

1. Introduction

Neuropsychiatric disorders are currently being classified in non-overlapping categories, which is based on conventional clustering of qualitative symptoms. The neurobiological mechanisms of the individual symptoms of these disorders are not taken into account in this classification. For the development of new treatments and to understand these disorders better, gaining more knowledge on the underlying neurobiology is a crucial step forward. Furthermore, considering the occurrences of cross-diagnostic phenotypes, we may need to put emphasis on dimensions crossing the borders of current diagnostic categories rather than on diagnostic categories separately. For these reasons a paradigm shift is necessary in research that allows for classification of patients on the basis of quantitative biological parameters (Kas et al., 2018 in this issue). US and European institutes for mental health research funding have already taken the first steps to initiate this paradigm shift in research by emphasizing this in new initiatives (Cuthbert and Insel, 2013; Haro et al., 2014). This is especially important as the burden of neuropsychiatric disorders increases every year and major advances in treatment have lacked behind in the last decades. This is in contrast with diseases like cancer, cardiovascular and infectious diseases where death rates have fallen and new treatment strategies are plentiful and effective (Cuthbert and Insel, 2013; Vigo et al., 2016; Whiteford et al., 2013).

One example of a symptom that crosses the borders of several neuropsychiatric disorders is sensory processing dysfunction (Danjou et al. in this special issue). Sensory processing deficits are common in multiple neuropsychiatric disorders, such as schizophrenia (SZ), attention deficit hyperactivity disorder (ADHD), and autism spectrum disorder (ASD) (Brown et al., 2002; Javitt and Freedman, 2015; Kas et al., 2007; Miller et al., 2009). Furthermore, comorbidity between these disorders is common. Multiple studies have found that adults with neuropsychiatric disorders like SZ were also diagnosed with ASD or had ASD symptoms during childhood (Mouridsen et al., 2008a,b; Unenge Hallerbäck et al., 2012). Both genetic and environmental factors are important in the early formation and fine-tuning of brain circuits necessary to receive, organize, and respond to sensory input in order to behave in a meaningful and consistent manner (Fig. 1). Understanding the neurobiological mechanisms underlying these sensory processing deficits will be important to identify targets for novel intervention strategies directed at neural circuit deficits. For those reasons, we will provide a review of the biological basis for (abnormal) sensory cortex development, multisensory integration, and behavioral responsivity. First, the neurodevelopmental trajectory of the sensory circuitry will be described and related to some risk gene mutations, in particular cell adhesion molecules, that are found across the neuropsychiatric

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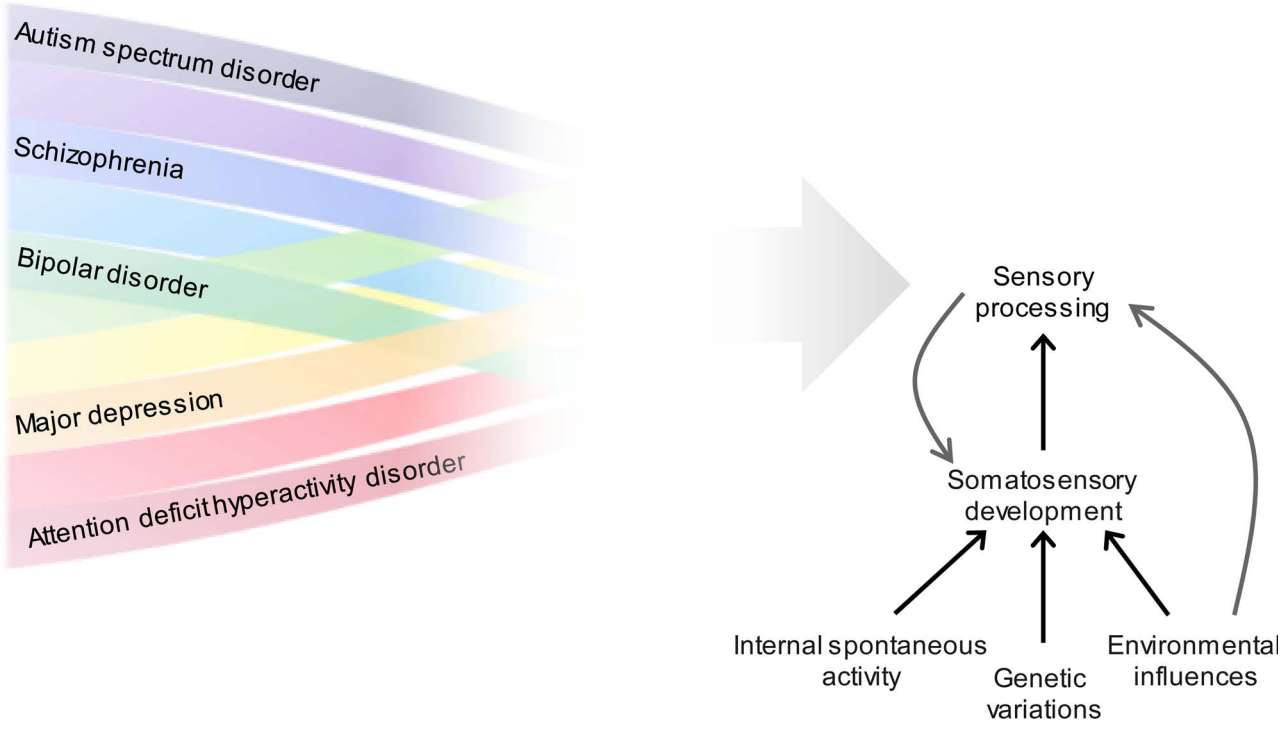

Fig. 1. Schematic model showing the relationship between the different factors influencing sensory processing and the neuropsychiatric disorders with sensory processing problems.

spectrum. Subsequently, the flow of sensory information through these circuits and the relationship to synaptic plasticity will be described. Finally, the current gap in knowledge to bridge our understanding of sensory processing deficits as a core feature of neuropsychiatric disorders will be addressed.

2. Somatosensory development

2.1. Cerebral cortex development

The development of the cerebral cortex starts after the closure of the neural tube with the formation of the ventricular zone (VZ) out of the first cells that migrate radially from the neuroepithelium (Angevine Jr. et al., 1970; Bystron et al., 2008). These neuroepithelial cells (NECs) undergo many symmetrically cell divisions to increase the surface area and thickness of the VZ (Rakic, 1995). After these cell divisions, NECs switch to asymmetrical cell division, which initiates the beginning of the neurogenesis and the generation of apical radial glial cells (aRGCs) (Huttner and Brand, 1997; Namba and Huttner, 2017). Just like NECs, aRGCs are attached to both the ventricle and the basal lamina (Huttner and Brand, 1997). A new layer arises above the VZ, called the subventricular zone (SVZ), that consists of intermediate progenitor cells (IPCs) that are not attached to the ventricular surface (Angevine Jr. et al., 1970). Many of the cells in the SVZ originate from asymmetrically dividing aRGCs, including IPCs, and will end up as cortical neurons (Noctor et al., 2004). IPCs divide symmetrically a couple of times to expand the pool of IPCs before they divide asymmetrically for a last time to produce two cortical neurons (Noctor et al., 2004).

These initial steps in the cortical development are orchestrated by gradients of signaling molecules in the cortex (See review by Govindan and Jabaudon, 2017). In absence of these so-called morphogens, such as *Pax6*, *Fgf10* and retinoic acid, cytodifferentiation is delayed or does not occur at all (Sahara and O'Leary, 2009; Siegenthaler et al., 2009; Tamai et al., 2007).

2.2. Neuronal migration and circuit development

The new postmitotic cortical neurons, which come from the IPCs and aRGCs, will migrate from the SVZ to their final destination in the cortical plate (CP) of the cortex (Angevine and Sidman, 1961; Sheppard and Pearlman, 1997). Neurons migrate by first extending their leading process, followed by the cell body and nucleus moving in line with the extended process causing it to retract again. Lastly, the trailing process retracts as well (Tsai and Gleeson, 2005).

Cajal-Retzius cells (CRs), originating from asymmetrically dividing aRGCs, migrate before the production of postmitotic neurons via the basal process of the RGCs to the marginal zone (MZ) (Meyer et al., 1998). Postmitotic neurons first use multipolar migration to reach the RGCs. Here they migrate via the basal process of the RGC, which is called radial migration or locomotion (Nadarajah et al., 2001; Rakic, 1972). When the leading process reaches the MZ of the cortex, the neuron migrates independent of the RGC to its final destination, a migration referred to as terminal or somal translocation (Nadarajah et al., 2001; Sekine et al., 2014). CRs secrete the extracellular protein Reelin that has multiple roles in the migration of neurons (Ogawa et al., 1995). Reelin and its many downstream factors, such as disabled-1 protein (Dab1) and cell adhesion molecules (CAMs), regulate the orientation of neurons towards the pial surface, the change in migratory mode from multipolar to radial, the terminal translocation, the termination of neuronal migration, and the aggregation of neurons in the cortical plate (Franco et al., 2011; Hiesberger et al., 1999; Howell et al., 1999; Jossin and Cooper, 2011; see review by Santana and Marzolo, 2017). Mice heterozygous for Reelin perform poorly in multiple behavioral tests related to autistic and schizophrenic traits. These behavioral impairments are a result of deficits in, among others, sensory processing. These behavioral deficits can be rescued by Reelin supplementation (Laviola et al., 2009; Rogers et al., 2013; Tueting et al., 1999). Mice with no functional *Dab1* gene show severe impairments in motor coordination paradigms that are associated with changes in brain structures, such as the cerebellum, thalamus, basal ganglia, visual and limbic networks (Jacquelin et al., 2013; Lalonde and Strazielle, 2011). Interestingly, while the organization and lamination of the cortex is affected,

loss of Reelin does not affect the somatotopic representation of the sensory periphery in the barrel cortex (Guy et al., 2015). It could be that tangential organization and circuit development between the thalamus and cortex are not influenced by Reelin. In addition to extreme neurodevelopmental conditions like lissencephaly, Reelin has been associated with neuropsychiatric disorders like SZ, ASD, and bipolar disorder (BD) (Ishii et al., 2016). Multiple studies found reduced protein and mRNA expression levels of Reelin in postmortem brain analyses in SZ, ASD, BP, and major depressive disorder (MDD) compared to controls (Fatemi et al., 2000; Impagnatiello et al., 1998; Torrey et al., 2005). Furthermore, some single nucleotide polymorphisms (SNPs) in the Reelin gene have been associated with SZ, ASD and ADHD. However, the contributions of these genetic variants to disease phenotype seem to be dependent on ethnicity and gender (Chen et al., 2017; Ishii et al., 2016).

In mammalian neuronal migration the oldest neurons are located more closely to the ventricles than the younger neurons that migrate over the older neurons to the pial surface of the cortex (Rakic, 1974). Whereas in non-mammalian vertebrates the opposite happens (Goffinet et al., 1986). This difference between mammalian and non-mammalian vertebrates could be explained by the scarcity of CRs and Reelin in non-mammalian vertebrates that drive the migration of mammalian neurons over relatively large distances in mammals (Goffinet, 2017). In the end, six layers have been formed in the CP of the cortex (Molnár et al., 2006). The aforementioned morphogens play a big role in the layering of the cortex. Different morphogens are situated in different layers and even specific types of neurons (Lein et al., 2007; Magdaleno et al., 2006; Molyneaux et al., 2007; Sugino et al., 2006). Many of these morphogens have functionally been tested with knock-out mouse models to see whether this specific expression pattern impacts layer and cell differentiation in the cortex. Indeed, Tbr1 is specific for layer 6 in the cortex and loss of Tbr1 hampers the differentiation of layer 6 (Bedogni et al., 2010). In *S*ox5 null mice the downregulation of *Fefz2* and *Bcl11b* expression in layer 6 and subplate is disturbed. Consequently, the maturation, migration, and differentiation of both layer 6 and subplate neurons is not complete (Kwan et al., 2008).

At the end of neurogenesis and migration, the circuitry between neurons starts to develop, which is an ongoing process that continues into adolescence. First, the neurites of the young neurons differentiate into long-distance projecting axons or multiple short dendrites (Craig and Banker, 1994). The fate of each neurite is determined by multiple intra- and extracellular signals. The exact processes controlling neurite fate is, however, still not completely understood (See review by Yogev and Shen, 2017). During axonal growth, the tip of the axon contains a growth cone that is guided into the proper direction by intrinsic mechanisms and signals from the surrounding tissues. These signals can attract or repel the growth cones and can originate from nearby or distant tissues (Tessier-Lavigne and Goodman, 1996). They can be membrane bound or secreted and form a gradient to guide the axons to the proper location. Some of the most prominent and well-studied axon guidance proteins are ephrins, netrins, Slits, and semaphorins (See review by Dickson, 2002). Ephrins help with the development of the topographical map of retinal axons (Cheng et al., 1995; Drescher et al., 1995). Netrins attract axons ventrally to the midline and deflect some axons (Culotti and Merz, 1998). Slits act as a midline repellent for axons (Brose et al., 1999). Next to this repellent role, slits also play a role in sensory axon branching and elongation (Wang et al., 1999). Lastly, semaphorins repel axons by acting as inhibitory cues at short distances (Cheng et al., 2001). All these axon guidance proteins are well conserved across vertebrates (Dickson, 2002). Next to these specific axon guidance proteins, more general chemoattractants and chemorepellents like Shh, Bmp and Wnt are also involved in the guidance of axons (See review by Pfaff and Shaham, 2013).

When the axon reaches its target, which are immature dendritic spines in the cortex, the growth cone changes its morphology and becomes a presynaptic axon terminal. In addition to this connection at the leading end of the axon with dendrites, axons also make contact with dendritic growth cones along the entire length of the axon (Vaughn, 1989; Ziv and Garner, 2004). Even before the mature synaptic structures are present, synaptic transmission is already present between neurons in hippocampal primary cultures (Ahmari et al., 2000). During synapse maturation, vesicles containing active zone molecules fuse with the presynaptic membrane to build up the active zones in the membrane (Maas et al., 2012; Tao-Cheng, 2007; Zhai et al., 2001). Synaptogenesis is a very heterogeneous process. Synaptic connections are built and broken down again, and various compartments within a synapse will change over time (See review by Garner et al., 2002). Whether a connection between an axon and a dendrite will survive might depend on the match between recognition molecules on the opposing membranes and the stabilization capacity between the membranes. For example, presynaptic membranes only express nectin-1, while postsynaptic membranes express nectin-3. These two have a higher heterophilic binding affinity for each other than a homophilic one for themselves. In this way they can promote axodendritic connections and block axon-axon and dendrite-dendrite connections (Togashi et al., 2006). Many other CAMs play a role in the formation and maturation of synapses, such as cadherins, integrins, neurexins, and synaptic CAM (See reviews by de Wit and Ghosh, 2016; Li and Sheng, 2003). The cadherin and neurexin CAM super families will be discussed in more detail below.

The cadherin superfamily consists of type-1 transmembrane glycoproteins with several cadherin motifs in the extracellular region. These cadherin repeats can make Ca^{2+} dependent heterophilic and homophilic interactions (Takeichi, 1988). In addition to the classical cadherins like N-cadherin and E-cadherin, the family consists of protocadherins and cadherin-related neuronal receptors (Hulpiau and Van Roy, 2009). N-Cadherin is a well-studied example that forms homophilic interactions at axodendritic connection sites (Huntley and Benson, 1999). In the absence of N-cadherin synaptic differentiation still occurs, but it is not complete (Togashi et al., 2002). When N-cadherin expression is inhibited, spine morphogenesis is abnormal, spines are shorter, and the number of mature spines is decreased (Mysore, 2007; Togashi et al., 2002). Via their interaction with catenins, classical cadherins mediate further synapse differentiation and maturation by recruiting specific proteins and receptors, via signaling pathways like Wnt, RHoA GTPase, and Hedgehog (Elia et al., 2006; Heuberger and Birchmeier, 2010; Lien et al., 2006). The expression of cadherins in the brain is very heterogeneous. Subtypes are only expressed in specific brain areas and layers (Krishna et al., 2011; Vanhalst et al., 2005). On a closer look, the expression in these regions is even more specified to specific networks or even specific types of cells, and the expression changes over time (Kim et al., 2007; Redies, 2000). One cell can express multiple cadherins and next to homophilic interactions, heterophilic interactions between different cadherins are observed (Hirano and Takeichi, 2012). Based on these observations, the hypothesis at the moment is that this cadherin code is different per neuron type and that this code gives every cell a very specific adhesion code that directs the synapse formation by attraction and avoidance between neurons and neurites (Hirano and Takeichi, 2012; Yagi, 2012). As there are more than 100 different cadherins, and they also have different isoforms, this code can be very sensitive. One can imagine that when a certain cadherin is mostly expressed in areas involved in sensory processing that in its absence, sensory circuit development and processing will be affected. The expression of protocadherin 7 and 9 (*Pcdh7* and *9*) is high in the primary somatosensory (S1) cortex and in the connecting thalamic ventroposterior nucleus (VP) (Kim et al., 2007). *De novo*, inherited copy number variations and a downregulation of transcription levels in lymphoblasts of *PCDH9* were found in ASD patients (Bucan et al., 2009; Girirajan et al., 2013; Leblond et al., 2012; Luo et al., 2012; Marshall et al., 2008). In addition, a SNP in the *PCDH9* gene has been linked to MDD in a meta-analysis of GWAS studies (Xiao et al., 2017). Loss of Pcdh9 in mice leads to changes in the morphology and number of

dendritic spines and reduces the thickness of the cortex area S1. In addition, these mice show deficits in social recognition, sensorimotor performance, and sensory gating (Bruining et al., 2015). Other cadherins have also been linked to several neuropsychiatric disorders. Indeed, many have been linked to ASD, and several of these cadherins have also been associated with BD and SZ, such as *CDH7*, *CDH12*, *CDH18* and *PCDH12* (See review by Redies et al., 2012).

Another CAM family consists of three neurexin genes that each have a short α and a long β isoform. Harkin et al. studied gene and protein expression levels of neurexins in human embryonic tissue. They found that gene expression levels of neurexin 1 (*NRXN1)* increases during embryonic development, *NRXN2* and *NRXN3* stay somewhat stable over time at, respectively, high and low expression levels (Harkin et al., 2017). Neurexins have numerous alternative splice variants (Treutlein et al., 2014). These splice variants show unique temporal and spatial expression patterns in the brain (Jenkins et al., 2016; Schreiner et al., 2014). However, the specific expression pattern of each splice variant in the different cortical layers has not been studied yet. Neurexins are mostly located in the presynaptic membrane and promote synaptic differentiation by interactions with other CAMs, including neuroligins, on the postsynaptic membrane (Dean et al., 2003; Graf et al., 2004; see review by Krueger et al., 2012). In the absence of neurexins, axons still seem to find their way to their targets (Budanova et al., 2007). Synaptic transmission, however, is disrupted in neurexin knockout mouse models and causes a high perinatal death rate (Missler et al., 2003). Members of the neurexin family have also been associated with neuropsychiatric disorders, such as ASD and SZ (See review by Reichelt et al., 2012). Several studies have examined the social and sensory characteristics in mice lacking the *Nrxn1α* gene. Unfortunately, the results have been inconsistent making it challenging to relate specific phenotypes to the *Nrxn1α* gene (Esclassan et al., 2015; Etherton et al., 2009; Grayton et al., 2013). Related to this, the role of specific neurexin isoforms or splice variants in specific aspects of sensory circuit development and processing has yet to be examined.

2.3. Development of projections between cortex and thalamus

The thalamus plays a major role in sensory processing (see chapter 3.1 and Fig. 2). During development, the thalamocortical and corticothalamic axons are guided through the internal capsule. Corridor cells and other neurons in the internal capsule, the striatum, cortex, and thalamus express or secrete morphogens to guide the axons (See for a review Garel and López-Bendito, 2014). Below, some examples for these axonal pathfinding mechanisms are provided.

Neurons in the VP express the Epha4 receptor in a gradient fashion; medial neurons have a high expression and lateral neurons have a low expression. Its counterpart, ligand Efna5, has a similar medial to lateral gradient in the cortical region that will later form S1 (Vanderhaeghen et al., 2000). When *Epha4* and *Efna5* are genetically deleted, many neurons are scattered around the normal cluster in VP and S1. This is especially the case for the medial neurons that have a high *Epha4* expression (Dufour et al., 2003). The expression of *Efna5* is particularly high in layer 4, 5 and 6 of the S1 cortex (Vanderhaeghen et al., 2000) (Fig. 3). Cortical axons are attracted by Sema3c that is released by cells in the SVZ. However, they do not penetrate the intermediate zone and the SVZ because the axons are repelled by Sema3a, which is secreted by cells in the VZ (Bagnard et al., 1998) (Fig. 3).

Thalamocortical projections are guided by pioneer projections from the cortex to the thalamus. Chen et al. showed that by preventing the growth of these projections, thalamic axons were still able to cross the internal capsule but when they reached the border of the cortex, the pallial-subpallial boundary (PSBP), the thalamic axons diverted and did not enter the PSBP. The cells in the lateral cortical stream of the PSBP direct the thalamic axons away when the cortical axons are not present (Chen et al., 2012). On the other hand, thalamic axons are necessary for the pioneer axons from the cortex to grow into the internal capsule. If the thalamic projections are absent, the corticothalamic axons will follow the trajectory that corticosubcerebral axons normally take to the cerebral peduncle (Deck et al., 2013). It seems that the cortical projections first reach the subpallidum and then wait there for one day before the thalamic projections reach that area (Métin and Godement, 1996). This waiting period is probably regulated by a change in transcription factors in the cortical axons destined for the cerebral peduncle and the thalamus. Deck et al. found that the Plxnd1/Sema3e complex is necessary to hold of the cortical axons to grow too early into the subpallidum (Deck et al., 2013).

Synchronous spontaneous activity is another mechanism that plays a role in the formation of the thalamus and cortex circuitries (Catalano and Shatz, 1998; Tang et al., 2003). Electrical activity and neurotransmitter release between cells in the developing nervous system contribute to the migration and connection between these cells (Yuste et al., 1995). For example, so-called retinal waves cross the retina before eye opening occurs. These retinal Ca^{2+} waves cause patterned neural activity in the visual cortex and other areas involved in the propagation of visual stimuli (Ackman and Crair, 2014). Ca^{2+} waves are also present in the thalamus before birth. These prenatal thalamic

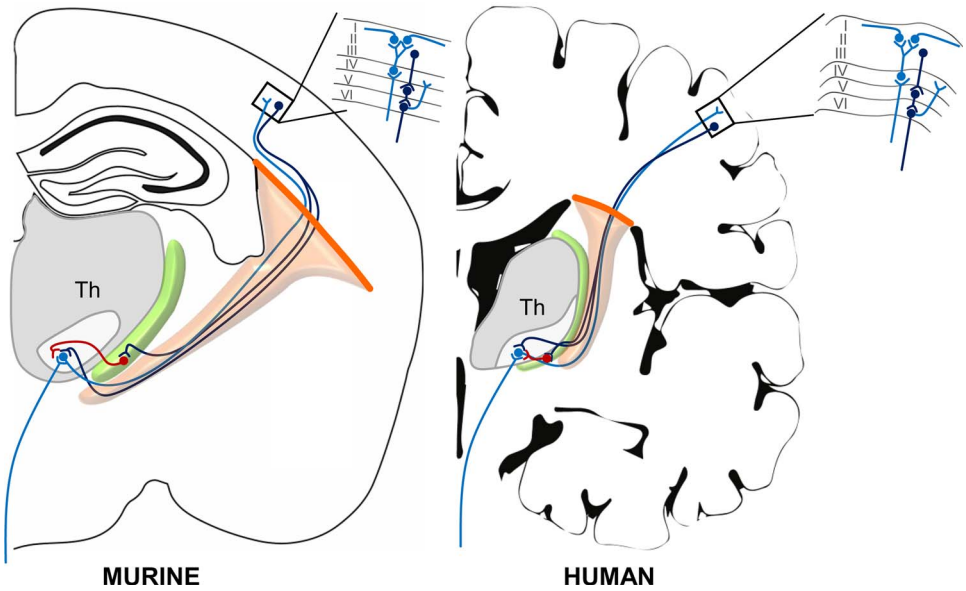

Fig. 2. Projections between somatosensory cortex and thalamus (Th) are shown in the adult murine and human brain, ventroposterior nucleus (VP) is highlighted. Ascending pathway (light blue projections) projects to the thalamic ventroposterior nucleus (VP) and goes via the internal capsule and striatum (orange) to cortex layer 4. There the information is passed on and a feedback loop (dark blue projections) goes back to the thalamus. One of the feedback axons first descends to the reticular nucleus (green) and sends inhibitory signals to the VP (red projections). The excitatory projections go directly to the VP. The bright orange line marks the pallial-subpallial boundary. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

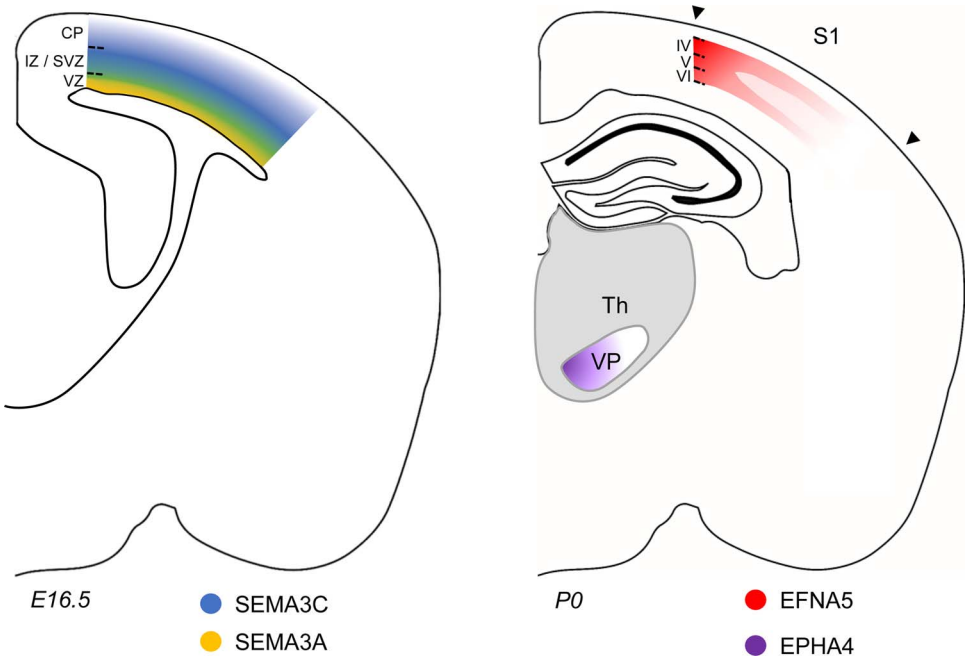

Fig. 3. Schematic representations of example morphogens involved in the guidance of thalamocortical and corticothalamic axons in the developing mouse brain. Left figure: Semaphorin 3C (SEMA3C) is released by cells in the subventricular zone (SVZ) and semaphorin 3A (SEMA3A) by cells in the ventricular zone (VZ) around embryonal day 16.5 (E16.5). Right figure: Around postnatal day 0 (P0) Ephrin receptor A4 (EPHA4) is expressed in a gradient fashion from medial (high expression) to lateral (low expression) in the thalamic (Th) ventroposterior nucleus (VP). Ligand ephrin A5 (EFNA5) is expressed in a gradient fashion from medial (high expression) to lateral (low expression) in layer IV, V, and VI of the primary somatosensory cortex (S1).

waves are transmitted from one sensory nuclei of the thalamus to another and they even propagate up to the cortex. In this way, different nuclei in the thalamus communicate with each other and disturbances in the initiation and propagation of the waves cause changes in the size of cortical areas. Ca^{2+} waves target factors that play a role in thalamocortical branching and are sensitive for changes in Ca^{2+} levels (Moreno-Juan et al., 2017). In the cortex the Ca^{2+} waves are initiated in the ventrolateral piriform cortex and then travel through the cortex (Lischalk et al., 2009). It seems that higher levels of asynchronous activity in this region together with gap junction functioning plays a role in the initiation of Ca^{2+} waves (Barnett et al., 2014).

3. Sensory cortex processing

Neurodevelopmental processes do not stop at birth, but continue until early adulthood (Marín, 2016). During this period the development is influenced by stimuli from outside as well as the behavioral state of the individual, and requires proper processing of external and internal (proprioception) sensory stimuli. Even after the overall neurodevelopment is complete the brain is still very plastic, allowing sensory stimuli to further influence ongoing developmental processes (Lövdén et al., 2013; Takesian and Hensch, 2013). There are many indications that sensory processing is affected in different neuropsychiatric disorders (e.g. Engel-Yeger et al., 2016). Until now, research on the mechanisms and networks behind sensory processing dysfunction has mostly focused on ASD and SZ (Javitt and Freedman, 2015; Thye et al., 2017). Other neuropsychiatric disorders, such as Alzheimer's Disease (AD) and MDD, have mostly been studied at the level of memory, cognition, and social aspects and not specifically on the basic mechanisms of sensory processing dysfunction. Below, we will discuss sensory processing from different perspectives and describe findings highlighting how sensory processing is disrupted in specific neuropsychiatric disorders.

3.1. Processing incoming sensory stimuli

The processing of sensory input consists of two phases; namely, to direct the person's attention to the region of interest in the surrounding environment, and then to decode this information to start the processing of that information (Gomez-Ramirez et al., 2016; Romo and Salinas, 2001). Receptors at the sense organs are sensitive for specific stimuli and are classified as chemoreceptors, mechanoreceptors, photoreceptors, and thermoreceptors (Francis-West et al., 2002; Singer et al., 2009). Each of these classes are divided in different subcategories such as for example, motion, stretch or vibration (Johnson, 2001). Somatosensory and auditory stimuli are first processed by relay neurons in the brainstem where rough separation of signals takes place (Angeles Fernández-Gil et al., 2010; Skoe and Kraus, 2010). Then the signals are sent to the thalamic nuclei specific for visual (lateral geniculate nucleus), auditory (medial geniculate nucleus), and somatosensory (ventroposterior nucleus, Fig. 2) stimuli (Sherman, 2016). In these thalamic regions the stimuli are further decoded in, for example location, pitch, intensity, or shape, and are subsequently relayed to cortex layer 4 (Friedman et al., 2004; Jones et al., 1982). In each area, cortical and subcortical, the receptive topography of the periphery is maintained in several modality maps. This means that the neighboring cells in the skin project to neighboring groups of neurons in areas such as the thalamus and cortex (Lenz et al., 2002; Simons and Woolsey, 1979). After the primary sensory cortex, the signal is send to secondary, higher-order areas. These secondary areas project to one of the major multimodal association areas in the cortex that integrate the signals from the different senses. Multisensory integration will be discussed in more detail in Section 3.3. Besides the layering of the cortex, it is also divided into columns in a radial fashion throughout all layers. Neurons belonging to one column most of the time have a similar function like orientation preference or ocular dominance (Haueis, 2016; Mountcastle, 1997). At each level in the system, the information becomes more specific and more complex; each postsynaptic neuron gets an even more specific task. In this way, the spatial organization and descriptive meaning of the stimuli becomes increasingly more vague and more concerned with the behavioral importance of these stimuli (See review by Bednar and Wilson, 2016). Finally, the information is send to other areas in the brain, for example, to store the information (hippocampus) or to induce action (through the motor cortex). Serotonin is one of the neurotransmitters that plays a role in the patterning of the primary sensory areas in the cortex as it alters and delays the sensory map maturation (Miceli et al., 2013). Siemann et al. tested mice with a gain-of-function variant of the serotonin transporter (SERT) gene in a multisensory paradigm. In contrast to their wild-type littermates, the *SERT* mutant mice did not perform better under multisensory conditions (Siemann

et al., 2017). Related to these observations, aberrations in the serotonergic system have been linked to several neuropsychiatric disorders, including ASD and MDD (See reviews by Andrews et al., 2015; Muller et al., 2016).

There are also tracts that project back to the thalamus from the somatosensory cortex (Jones, 1975). For a long time the exact function for this feedback loop was not clear and there is still much that needs to be investigated. Most of the projections to the thalamus, even more than those coming from the periphery, come from feedback neurons in cortex layer 6 (Liu et al., 1995; Liu and Jones, 1999). These feedback neurons have axons that terminate in the thalamus and also in other layers of the cortex. They have an excitatory and inhibitory effect on the relay neurons that channel the information from the sensory organs to the cortex (Liu et al., 1995). The excitatory effect works via a direct pathway but the inhibitory effect takes place by stimulating relay neurons in the reticular nucleus of the thalamus and these reticular relay neurons inhibit neurons in the VP (Jones, 1975) (Fig. 2). It seems that this feedback loop has two main functions in sensory processing. The first one is to refine the receptive fields and tune the thalamic neurons. The second function is to improve the transmission of sensory signals from the sense organs to the cortex (See review by Briggs and Usrey, 2008).

Many studies show that ASD patients have low long-distance connectivity and high local connectivity (Belmonte et al., 2004; Kana et al., 2011; Wass, 2011). These disruptions are mostly found in late developing cortical regions. The severity of this dysconnectivity correlates with the severity of ASD (Barttfeld et al., 2011; Keown et al., 2013; Kikuchi et al., 2015). One discrepancy in the long-rang under-connectivity is that several studies have reported an increase in thalamo-cortical projections and cortical-subcortical connections (Wass, 2011). Besides ASD, other neurodevelopmental disorders like ADHD and Tourette Syndrome show similar connectivity abnormalities (Kern et al., 2015). Dysconnectivity is also found in SZ (O'Donoghue et al., 2017). The multimodal network in SZ patients is less efficiently wired than in healthy subjects (Bassett et al., 2008). Ordóñez et al. reviewed studies that compared children with onset of psychosis and SZ before the age of 13 and their not affected siblings by fMRI analyses (Ordóñez et al., 2016). They conclude that in these children with SZ the local connectivity strength is disrupted. Brain network analyses in, for example, MDD and social anxiety (SAD) have mostly found alterations in the default mode network and limbic system (Brakowski et al., 2017; Kim and Yoon, 2017; Wang et al., 2012). Overall, the data available on brain connectivity in neuropsychiatric disorders is not conclusive and not specifically directed at sensory processing. Systematic investigations into the connectivity between and within the sensory systems correlated with sensory processing dysfunctions in neuropsychiatric disorders are therefore necessary.

3.2. Sensory gating

The brain first processes all sensory stimuli subconsciously. This pre-attentive filtering of incoming information is termed sensory gating (Braff and Light, 2005). One way to measure this is by recording the event-related potentials (ERPs) with electroencephalography (EEG) to different stimuli. Subconscious ERP responses are believed to happen 40–80 ms after a stimulus (Freedman et al., 1983). In the P50 suppression paradigm, repeats of paired clicks with an interval of 500 ms between the two clicks are presented. Normally the response 50 ms (P50) after the second click is lower than the P50 after the first click (Freedman et al., 1983; Light and Braff, 2003). Many studies have been published on P50 suppression disturbances in SZ and BD patients (See meta-analyses by Cheng et al., 2016; Patterson et al., 2008). Prepulse inhibition (PPI), pre-attentive inhibition of the startle reflex by a preceding weak sensory stimulus, and mismatch negativity (MMN), pre-attentive orientation to a deviant stimulus in a series of repeated stimuli that are the same, are also paradigms to measure components of sensory gating (Erickson et al., 2015; Light and Braff, 2003). Both are affected in SZ and BD patients (Braff et al., 2001; Erickson et al., 2015). Interestingly, it seems that BP patients that are not in a manic episode show normal PPI (Barrett et al., 2005). This elicited the hypothesis that sensory gating dysfunction is related to psychosis and the finding of normal PPI in MDD corroborated this (Perry et al., 2004; Quednow et al., 2006). However, it is becoming clear that sensory gating, including PPI, is also impaired in several non-psychotic disorders, such as AD, ASD, and obsessive compulsive disorder (OCD) (Ahmari et al., 2012; Kohl et al., 2013; Sinclair et al., 2016; Thomas et al., 2010). Even MDD patients seem to show impaired MMN processing (Mu et al., 2016). Abnormalities in different neural networks can be the cause for sensory gating dysfunction across the neuropsychiatric spectrum (Kohl et al., 2013; Mayer et al., 2009). For example, the cortico-striato-thalamo-cortical circuitry involved in PPI is also linked to the inhibitory dysfunction in OCD (Ahmari et al., 2012; Geyer and Dulawa, 2003; Kohl et al., 2013; Maia et al., 2008). Another example is the involvement of the cholinergic system in sensory gating, and neuropsychiatric disorders like SZ and AD (Adler et al., 1998; Court et al., 2001; Lucas-Meunier et al., 2003; Thomas et al., 2010). Additional methodologies to assess sensory processing deficits across diagnoses (e.g., SZ and AD), will be addressed in another manuscript as part of this special issue (Danjou et al., 2018 in this issue).

3.3. Multisensory integration & dysfunction

Multisensory integration may facilitate stimulus detection. When two or more sensory modalities are presented at once, they will enhance or depress each other's effect. Different neurons and different cross-modal stimulus combinations to the same neuron changes the extent of multisensory integration. Sensory information is always processed with a comparison of background inputs in any circumstance, also when the information is not useful for that circumstance (Stein and Stanford, 2008). This makes the processing of multisensory information even more difficult, and makes it even more intriguing that most of the time we are unaware of this cross-modal integration of sensory information. Binding of sensory stimuli of different modalities takes place when determinants like place and time correspond between these stimuli. Coinciding weak stimuli enhance the integrated response signal significantly. While two coinciding strong stimuli are already easy to focus on and therefore the integrated response signal is not further strengthened. This phenomenon is called inverse effectiveness (Meredith and Stein, 1986; Stanford and Stein, 2007). When the stimuli do not concur and the opposing signal is strong enough it produces a response depression. The time between the stimulus entry, sensory encoding, and motor response is shorter when multiple overlapping modalities are integrated (Calvert and Thesen, 2004; Nozawa et al., 1994; Stein and Stanford, 2008).

Multisensory integration takes place within and between the sensory regions in the cortex and in some subcortical areas. For example, visuotactile integration happens between the primary visual and the somatosensory cortices in the rostral lateral area (RL) (Olcese et al., 2013). Olcese et al. mapped the RL area by multiunit recordings in mice. They found that in this area neurons are present that respond to unimodal stimuli and multimodal stimuli. The visual receptive field is better represented in this area than the tactile field. Furthermore, multisensory enhancement is more visible at the level of action potentials (outputs) than at the level of post-synaptic potential (inputs).

For a long time the assumption was that stimuli are first processed in cortical areas corresponding to the sense organ and afterwards relayed to multisensory regions. Lately, it is becoming more clear that multisensory integration happens in parallel to unisensory processing (Calvert and Thesen, 2004). The superior colliculus (SC) plays a central role in multisensory integration, especially while guiding someone's attention or behavior to a certain location (Meredith and Stein, 1983; Stein and Stanford, 2008). The visual modality seems to be at the center

of this. By moving someone's eyes to one point in space, both auditory and tactile attention will also shift in that direction (Groh and Sparks, 1996; Jay and Sparks, 1984). Just like in the RL area, the sensory receptive fields are also projected in the SC (Kadunce et al., 2001). In the posterior parietal cortex of primates, multisensory information is integrated to shift the gaze and direct limb movements (Cohen and Andersen, 2002; Stein and Stanford, 2008; Stricanne et al., 1996). Not much is known about other multisensory integrations besides spatial and temporal integration.

The development of multisensory integration networks starts after birth. While the multisensory neurons are already present in monkeys at birth in the SC, they are not yet capable of integrating cross-modal inputs (Wallace and Stein, 2001). Also humans are not able to integrate multisensory cues at birth. This process starts to develop in the first year of life (Neil et al., 2006). The importance of these first months for multisensory development has been shown in individuals that were born with binocular cataracts and had it corrected at least 5 months after birth. This congenital visual deprivation impaired audio-visual integration in these individuals, while unisensory visual performance is not affected (Putzar et al., 2007).

In multiple mouse models related to ASD, multisensory integration is impaired and this seems to be caused by impaired integration in the insular cortex, a multifunctional center in the brain where sensory, emotional and cognitive content is integrated. The insular cortex has a delay in maturation in these mouse models, especially the inhibitory circuitry seems to be affected. This delay in maturation can be compensated for by administering a benzodiazepine agonist, diazepam, during juvenile age (Gogolla et al., 2014). While typically developing (TD) children benefit from multisensory inputs, like the combination of a tone and a light-flash, children with ASD do not (Brandwein et al., 2013). This has also been found in a SERT Ala56 knock-in autism mouse model, that underwent a multisensory testing paradigm similar to that used in humans (Siemann et al., 2017). The SERT Ala56 is a gene variant of the human serotonin transporter that has been linked to ASD and sensory processing dysfunction (Muller et al., 2016). Because of multisensory integration, cross-modal illusions are also possible (Stein and Stanford, 2008). One example is that when a single light-flash is combined with two beeps, a person will perceive this as a double flash. Another example is the rubber hand illusion. It has been shown that ASD children are initially less susceptible to this illusion than TD children (Cascio et al., 2012). The dysfunction in multisensory integration in ASD seems to fade away when they get to adolescence (Foxe et al., 2015). Recently two studies were published, showing hyperintegration of temporally unmatched audio and visual cues in SZ patients (Stevenson et al., 2017; Zvyagintsev et al., 2017). In contrast, SZ patients are less susceptible to illusions compared to healthy controls (Vanes et al., 2016; White et al., 2014). These results corroborate findings in unisensory integration tasks that show that SZ patients are hypersensitive in explicit tasks (e.g. temporal asynchrony) and less susceptible for implicit tasks (e.g. illusions) (Lalanne et al., 2012). While multisensory integration has been studied in ASD and SZ, these kind of studies are difficult to find in other neuropsychiatric disorders (De Gelder et al., 2005; Thye et al., 2017). One study reported that patients with mild cognitive impairment and AD also show a delay in audiovisual integration compared to normal aged controls (Wu et al., 2012). Furthermore, Panagiotidi and colleagues found that adults with high levels of ADHD-like traits have a shorter temporal audiovisual integration window compared to those with low levels of ADHD-like traits (Panagiotidi et al., 2017).

3.4. Social functioning

Social dysfunction is an apparent phenotype across the neuropsychiatric spectrum. While many processes, such as motivation and learning, contribute to the establishment of social behavior, the processing of external cues related to the social context may be another important factor to consider. All information provided by our surroundings, including the people and objects in it, is combined to form a wide range of sensory information entities that need to be processed. Social cues, for example, need to be interpreted by integrating facial expression, speech, body language etc. In this way, the absorption of social cues require already a high level of multisensory integration to prepare for an appropriate behavioral response. Both individuals with ASD and SZ, and also other disorders where sensory processing is affected, have difficulties in social settings. For example, this is generally expressed as high levels of social withdrawal, an (early) common symptom across the neuropsychiatric spectrum (Kas et al., 2018 in this issue). The exact mechanism that explains the link between sensory processing and social functioning in these disorders is not exactly known.

One region in the brain that may provide a connection between sensory processing and social cognition is the thalamus. As mentioned above, the thalamus is the relay center between the sensory periphery and the sensory cortex areas with a feedback loop back to the thalamus (Fig. 2). The thalamus also has projections to several regions in the limbic system like the anterior cingulate cortex (ACC) and the insula (Thye et al., 2017). These areas are involved in emotion processing, learning, memory, and interoceptive awareness. Furthermore, the size of the right insula cortex and left isthmus are positively correlated with poorer social behaviors in ASD (Doyle-Thomas et al., 2013; Nair et al., 2013; Wass, 2011). In addition, abnormalities in the function of the thalamus, insula and ACC are found in MDD and SAD patients while listening to praise or criticism (Hamilton et al., 2015). Another region in the brain that is involved in social cognition is the superior temporal cortex (STC). It plays a role in, for example, emotional recognition, understanding intention, and gaze detection (Narumoto et al., 2001; Pelphrey et al., 2004a,b). Furthermore, STC is involved in general multisensory integration (Loveland et al., 2008; Stevenson et al., 2011; Thye et al., 2017). The STC seems to be functioning abnormally in ASD patients and this has been linked to the STC functions like the ones listed before, but also speech perception and affective touch processing (Kaiser et al., 2016; Redcay, 2008). In addition, temporo-thalamic overconnectivity was found in individuals with ASD using fMRI (Nair et al., 2013). In SZ patients, differences in these areas are found as well. SZ patients that undergo a test for humor processing, have more difficulties with distinguishing and finishing humoristic sentences and this is associated with decreased activity in the right posterior temporal cortex, left dorsomedial frontal cortex, and the ACC (Adamczyk et al., 2017). Mitelman et al. compared glucose metabolic rates in PET combined with MRI scans of SZ and ASD patients. They found that both showed similar changes in metabolic rates in brain areas that are associated with social cognition; the prefrontal cortex, visual cortices, amygdala, hippocampus, thalamic nuclei (pulvinar and ventral posteromedial) and basal ganglia structures (Mitelman et al., 2017). Also in MDD and BP similar brain structures and networks related to social cognition are impaired (Cusi et al., 2012).

That there is an association between sensory processing sensitivity and social functioning is becoming more clear nowadays. Indeed, both hyper- and hyposensitivity have been linked to higher levels of anxiety and depressive symptoms in different populations (Ben-Sasson et al., 2008 (ASD); Bitsika et al., 2016 (ASD); Engel-Yeger et al., 2016 (major affective disorders); Engel-Yeger and Dunn, 2011 (healthy); Pfeiffer et al., 2005 (Asperger's disorder); Serafini et al., 2017 (MDD & BP)). How these behavioral associations between sensory processing sensitivity and social functioning can be explained by abnormalities in the above mentioned neural networks in neuropsychiatric disorders has yet to be explored.

3.5. Synapse plasticity

As mentioned in the previous paragraphs plasticity of individual synapses, or more specifically the misregulation of this plasticity may

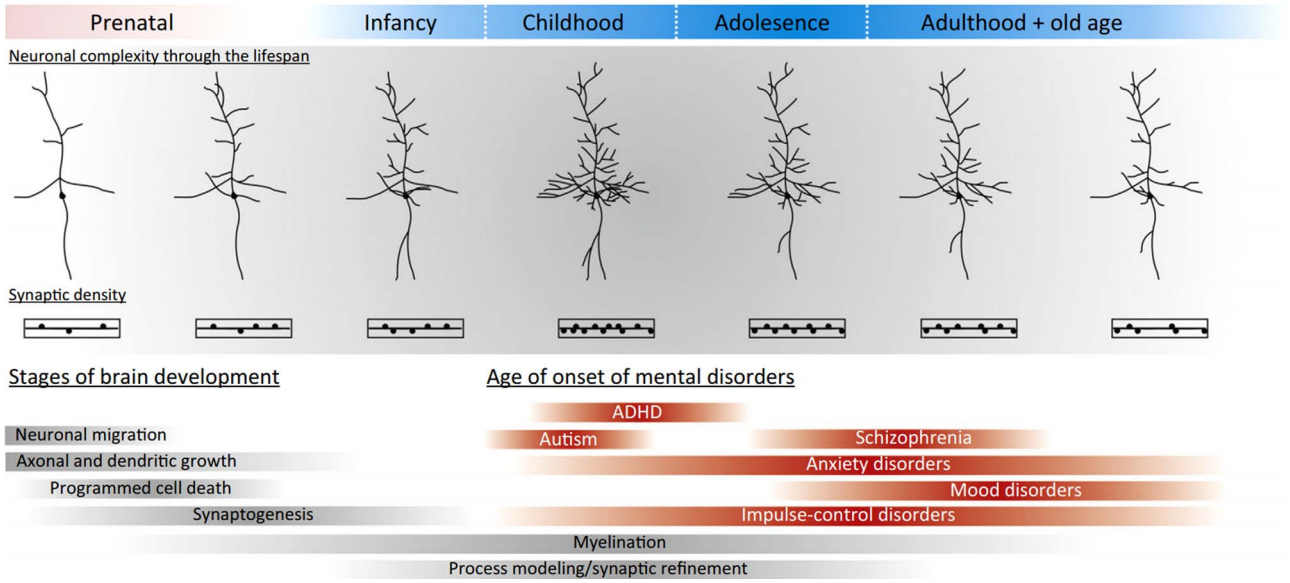

Fig. 4. Temporal profile of stages of brain development in relation to the age of onset of mental disorders. Early life perturbations (e.g., gene mutations, or environmental factors) can impact neurodevelopmental processes, such as neural circuits involved in sensory information processing, and potentially lead to adverse mental health outcomes later in life (adapted from (Borre et al., 2014)).

critically contribute to the observed deficits, such as in sensory information processing, associated with neuropsychiatric disorders. Human genetic screens have identified a series of genes that upon misregulation of its expression negatively impact spine plasticity and density. As mentioned earlier, morphological analyses of *Pcdh9* lacking-mice revealed an increase in spine density in the somatosensory cortex (Bruining et al., 2015). Whereas a loss of *Pcdh10* affected amygdala functioning and increased spine density in this region. Spine-type specific analyses suggested that the latter was a result of an increased number of filopodia in this region (Schoch et al., 2017). Haploinsufficiency of *Shank3*, a scaffolding protein, due to deletion or *de novo* mutation has also been linked to autism spectrum disorders (Peça et al., 2011). Mice lacking *Shank2* and *Shank3* exhibit impaired NMDAr-dependent synaptic plasticity, and it is interesting to note that *Pcdh10* mutant mice also have reduced levels of NMDAr subunits (Schoch et al., 2017). Because NMDA receptors are tightly connected to filamentous actin through actin-binding proteins, and the fact that loss of cadherin or shank genes leads to abnormal structural plasticity (*i.e.* misregulation of spine density) together these observations suggest that misregulation actin dynamics may play a central role in at least a number of neuropsychiatric disorders and indicate that the molecular machinery modulating actin dynamics may be valuable candidates to prevent the endophenotypes associated with ASD. Actin filaments continuously grow and shrink and this process is highly orchestrated by a series of positive regulators such as profilin and negative regulators including ADF/cofilin (Bernstein and Bamburg, 2010). These regulators are targeted by a larger series of signaling pathways including Rac1 and PKA raising the interesting question whether the abnormal structural plasticity could be prevented by targeting key downstream enzymes such as cofilin (Sarmiere and Bamburg, 2004). Indeed, recent work has shown that genetic inhibition of cofilin activity in hippocampal neurons is sufficient to prevent memory impairments, synaptic plasticity deficits, and spine loss associated with sleep deprivation and reverse the memory and plasticity phenotypes in mice expressing a mutant form of the BAF complexes (Havekes et al., 2016; Vogel Ciernia et al., 2017). Because loss of *Shank3,* just like sleep deprivation, leads to increased cofilin activity Duffney and colleagues assessed whether blocking cofilin function or activating Rac1 prevented social deficits and NMDAr hypofunction in these mutant mice (Duffney et al., 2015, 2013). Indeed, treatment with cofilin inhibiting peptide and activation of Rac1 were both sufficient to restore NMDAr function and prevent social deficits. Intriguingly, inhibition of PAK or Rac1 function leads to social deficits and NMDAr hypofunction in wild-type mice suggesting that misregulation of structural plasticity at the level of cofilin signaling critically contributes to some of the phenotypes associated with neuropsychiatric disorders. Moreover these findings further corroborate the potential of peptide therapeutics in reversing phenotypes with neurocognitive and neurodevelopmental disorders and raises the possibility that similar strategies can also successfully be used to reverse the behavioral and morphological phenotypes in other mouse models of neuropsychiatric disorders such as the cadherin mutant mice (Shaw and Bamburg, 2017). The question remains whether altered synaptic plasticity in the thalamus and/or cortex are contributing to the sensory processing deficits that can be observed across the diagnostic boundaries of neuropsychiatric disorders.

4. Future directions

4.1. Gaps in knowledge

Fundamental neuroscience research has provided novel insights in the way that neural circuits underlying sensory processing are being developed. Furthermore, understanding of the intrinsic and external factors that shape these circuits at particular stages of development is growing. Nevertheless, several critical questions related to sensory processing dysfunction in neuropsychiatric disorders remain. For example, what are the exact circuitries that are altered in patients suffering from sensory processing dysfunction, and are these deficits the same across the neuropsychiatric spectrum? And are these dysfunctions purely related to thalamocortical connections not being shaped properly during development, or are these, for example, dependent on different disease related pathologies? Assessment of a variety of sensory processing paradigms across neuropsychiatric disorders are necessary to address these questions. Once knowing the diversity of disease origin underlying sensory processing dysfunction(s), further understanding of the biological substrate will be important to develop etiology-directed treatment strategies to tackle these dysfunctions. Finally, assuming that the sensory deficits are core to the disease, what part of the behavioral profile observed in neuropsychiatric patients will be reversed following successful sensory processing interventions?

4.2. Potential treatment directions: windows for treatment opportunity

For most vertebrates, the majority of organs develop during embryogenesis and postnatal changes are mainly concerned with growth. However, the brain is different in that a considerable amount of brain structural changes also occur during the postnatal period (Fig. 4). For example, recent studies on cortical development, including synaptic remodeling, showed that this process continues well beyond adolescence and stabilizes in adulthood (Petanjek et al., 2011). The neuronal circuits that generate behavior are shaped by genes and the environment throughout life, but there are some stages at which brain development is particularly sensitive to experience (Hensch, 2005), so-called critical periods. Within these time-windows sensory experiences and intrinsic neuronal activities jointly shape normal development and refine neural circuits. Outside these windows, the brain is resistant to changes to the same stimuli. These key periods of high brain plasticity particularly during early life involve not only sensory systems, but also motor systems and cognitive processes (Kuhl, 2010). After these 'windows in development', the level of plasticity is reduced (Hensch, 2005, 2004). The question remains whether sensory processing dysfunction, that is observed in a wide variety of neuropsychiatric disorders, has to be reversed during these critical windows of development, or whether interventions later in life may be capable of reversing sensory processing deficits. Furthermore, understanding the neurobiological mechanisms underlying these sensory processing deficits will be important to identify targets for novel intervention strategies directed at these neural circuit deficits. For example, lack or dysregulation of a neurodevelopmental risk gene expression may lead to early life exaggerated brain plasticity processes (e.g., increased local protein synthesis and spine density) within the sensory circuit and subsequent aberrant behavior. To test these hypotheses, reactivation of the CAMs during their critical period of gene expression and targeted pharmacological intervention during periods of, for example, exaggerated protein synthesis should reverse sensory circuit dysfunction and prevent aberrant behavioral development later in life. Signaling molecules within the molecular pathway underlying exaggerated protein synthesis and that contribute to synaptic remodeling may be potential targets for these intervention studies.

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