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Review article

Individuals being high in their sensitivity to the environment: Are sensitive period changes in play?

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ABSTRACT

All individuals on planet earth are sensitive to the environment, but some more than others. These individual differences in sensitivity to environments are seen across many animal species including humans, and can influence personalities as well as vulnerability and resilience to mental disorders. Yet, little is known about the underlying brain mechanisms. Key genes that contribute to individual differences in environmental sensitivity are the serotonin transporter, dopamine D4 receptor and brain-derived neurotrophic factor genes. By synthesizing neurodevelopmental findings of these genetic factors, and discussing them through the lens of mechanisms related to sensitive periods, which are phases of heightened neuronal plasticity during which a certain network is being finetuned by experiences, we propose that these genetic factors delay but extend postnatal sensitive periods. This may explain why sensitive individuals show behavioral features that are characteristic of a young brain state at the level of sensory information processing, such as reduced filtering or blockade of irrelevant information, resulting in a sensory processing system that 'keeps all options open'.

1. Environmental sensitivity

1.1. Individual differences in environmental sensitivity

Environmental Sensitivity, which is defined as the ability to perceive, process and respond to environmental stimuli (Pluess, 2015), is one of the most basic individual characteristic across most species. This phenomenon is essential for survival, as without this ability, an organism would not be able to perceive and respond to various environmental conditions, whether these are of physical or psychosocial nature, and whether they are negative or positive (i.e., supportive for development and survival or threatening). Environmental sensitivity is at the root of virtually all behaviors and enables an individual to adapt to environmental changes. While all individuals on earth are sensitive to the environment, several theories (biological sensitivity to context, differential susceptibility, sensory processing sensitivity) (Greven et al., 2019; Pluess, 2015) and supporting empirical evidence suggest that they differ in the extent to which they are sensitive to environments. That is, some individuals are more sensitive and respond stronger to the same stimulus compared to others (Pluess, 2015; Wolf et al., 2008).

Research has shown that those who are highly sensitive, who we refer to as environmentally sensitive individuals, are typically characterized by an inhibited, careful exploratory, reactive and flexible behavioral style, as opposed to activated, bold, pro-active and rigid behavior of less sensitive individuals (Pluess, 2015). This is seen across species, from insects to mammals (Wilson DS et al., 1994). For instance, rodent research makes a distinction between mice and rats with proactive and reactive coping styles (Koolhaas et al., 1999), researchers of insects, fish and humans often use the terms shyness and boldness to denote individual differences in behavior (Sloan Wilson et al., 1994), and in bird research Hawks and Doves have been identified to denote aggressive fast explorers and non-aggressive slow explorers (Korte et al., 2005). In humans, the trait sensory processing sensitivity (SPS) (in layman terms: highly sensitive person) has been identified; those who are high in SPS are more sensitive and responsive to the environment (Aron and Aron, 1997). All these terms that researchers use to describe trait-like behavioral differences between individuals in a population basically refer to alternative responses to environmental stimuli that

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reflect a general, relatively stable tendency to perceive, process and respond to the stimuli over time and across various situations. Individuals who are reactive and shy and behave like doves pay attention and adapt their behavior to environmental changes, whereas proactive bold individuals show more rigid routine-like behavior (Benus et al., 1990). It is thought that such individual differences in behavior in a population reflect two different evolutionary strategies (plastic versus fixed) and both are the result of natural selection (Dall, 2004; Rands et al., 2003). Thus, while at the individual level some small behavioral changes are possible, a highly sensitive person is unlikely to turn into a low sensitive person and *vice versa*.

1.2. Relevance of environmental sensitivity

The existence of individual differences in environmental sensivity allows the population as a whole to function well under both stable and varying environmental conditions (Wolf et al., 2008). Of importance, individuals showing increased environmental sensitivity react stronger to both positive stimuli that benefit them, increasing positive functioning, and to negative stimuli that threaten them, increasing stress and vulnerability to stress-related problems (Aron et al., 2012; Belsky and Pluess, 2009; Greven et al., 2019; Lionetti et al., 2018; Piray et al., 2019). This makes environmental sensitivity of high interest for understanding individual differences in how we see the world around us, how we feel, how we respond to our constantly changing environment as well as for the refined understanding of phenotypes and personality, fitness with environment, and mental health and disease. The understanding of environmental sensitivity is relevant for (1) ecologists and evolutionary biologists who aim to understand the ecological function of individual variation in environmental sensitivity and its consequences for evolutionary fitness (Wolf et al., 2008), for (2) developmental psychologists who aim to understand the origin of personality differences, for (3) behavioral neuroscientists who intend to uncover gene–environment interaction in the development of phenotypes and the underlying neural and physiological mechanisms (Barr et al., 2003), and finally for (4) biomedical researchers who exploit individual differences in environmental sensitivity to understand disease vulnerability and work towards personalized medicine (Ginsburg and Willard, 2009). In addition, increased environmental sensitivity, specifically SPS, receives a lot of societal interest because it is highly recognizable and explains why some individuals feel that they are 'different' compared to others (Greven et al., 2019). Surprisingly, the brain mechanisms underlying increased environmental sensitivity are virtually unknown. Increased environmental sensitivity is speculated to be associated with a hypersensitive nervous system (Pluess, 2015). But what does this mean? The aim of this narrative review is to set out a hypothesis to direct future brain studies on individual differences in environmental sensitivity.

1.3. Overview review

Overall aim of review: In this review, we synthesize the way in which advancements in the understanding of the effects of factors increasing environmental sensitivity align with the mechanistic framework of sensitive period plasticity. We propose that these factors interfere with sensitive period plasticity and delay but extend sensitive periods, potentially explaining the enhanced environmental sensitivity.

Structure of review: We first describe, in humans and in animal models, the genetic (monoaminergic and neurotrophic) factors that confer increased environmental sensitivity (Section 2). Based on animal literature we subsequently explain what sensitive periods are, what the main neural mechanisms related to sensitive periods are (Section 3), and how sensitive periods are influenced by monoamines (Section 4). Next, again based on animal literature, we describe the effects of monoamines on brain development and show how these developmental changes can target mechanisms also implicated in sensitive periods (Section 5). Then we present sensitive period mechanistic (Section 6) and behavioral changes in animal models mimicking genetic variations associated with environmental sensitivity (Section 7). To turn back to human research, we explore connections between the molecular, cellular and physiological changes occurring during sensitive periods found in the animal models and those observed at the system level in humans (Section 8). And to raise the awareness that sensitive periods are not only influenced by factors that increase environmental sensitivity but that environmental sensitivity per se can also influence the sensitive periods, we describe the interrelationship between environmental sensitivity and sensitive periods (Section 9). Finally, we summarize the main message from this review and put forward suggestions for future research to follow-up the mechanistic proposal for increased environmental sensitivity (Section 10).

2. Genetic factors mediating environmental sensitivity

Environmental sensitivity is strongly related to plasticity. That is, highly sensitive individuals show behavioral phenotypes that are strongly shaped by the environment. Thus, due to increased sensitivity to both positive and negative environmental stimuli these individuals display highly adaptive behavioral responses in a for-better-and-for-worse manner. Of interest, a large twin study has demonstrated that increased environmental sensitivity has a significant heritability of 47%, meaning that the other 53% of variance is shaped by environmental factors (Assary et al., 2021). The genetic factors that have so far been associated with increased environmental sensitivity are genes related to monoaminergic and neurotrophin signaling (Belsky et al., 2022; Homberg and Jagiellowicz, 2022).

2.1. Serotonin transporter gene variance

There is converging evidence from neurobiological and psychological research that particularly serotonergic and dopaminergic genes are implicated in increased environmental sensitivity. For instance, in humans and non-human primates, the low activity short allelic variant of the serotonin transporter (5-HTT) linked polymorphic region (5-HTTLPR s-allele), as compared to the 5-HTTLPR long (l) allele, is seen as an exemplary gene variance for increased environmental sensitivity; it has been associated with heightened sensitivity to both negative and positive environmental stimuli in early life and adulthood (Babineau et al., 2015; Bakermans-Kranenburg and van Ijzendoorn, 2011; Beevers et al., 2010, 2011; Belsky et al., 2009; Belsky and Pluess, 2009; Flasbeck et al., 2019; Fox and Beevers, 2016; Fox et al., 2011; Homberg and Jagiellowicz, 2022; Homberg and Lesch, 2011) (but see (Dainer-Best et al., 2018; van Roekel et al., 2018; Weeland et al., 2015)) with for-better-and-for-worse outcomes. The s-allele has also been associated with increased flexibility (Jedema et al., 2010). In line with these human and non-human primate findings, rats and mice lacking the serotonin transporter (5-HTT) and modeling the 5-HTLLPR s-allele (Caspi et al., 2010b; Schipper et al., 2019) display, compared to wild-type controls, increased sensitivity to stress (for review, see (Carola and Gross, 2012)) and tactile stimulation (Roversi et al., 2020) in early life. These knockout animals also show increased sensitivity to (conditioned) rewards such as sucrose (Nonkes et al., 2012a, 2014), psychostimulants (Homberg et al., 2008; Nonkes et al., 2013; Verheij et al., 2017), co-housing with a female (Kastner et al., 2015), and environmental enrichment (Rogers et al., 2017; Sbrini et al., 2020) in adulthood. These animals furthermore exhibit increased behavioral and cognitive flexibility (Nonkes et al., 2013). Finally, it has been demonstrated that the human personality trait 'Openness to experience' is related to reduced cerebral 5-HTT levels (Kalbitzer et al., 2009).

2.2. Dopamine D4 receptor gene variance

For the dopaminergic system, there is strong support that the dopamine D4 receptor (DRD4) 7-repeat allele (Belsky et al., 2009;

Homberg and Jagiellowicz, 2022) affects the interaction with positive and negative experiences in a for-better-and-for-worse manner. For instance, the 7-repeat allele, compared to all other DRD4 allelic variants, was found to increase risk for disorganization in children exposed to maternal unresolved loss/trauma, but to decrease this risk in children exposed to mothers who had no unresolved loss (Bakermans-Kranenburg and van Ijzendoorn, 2011). As another example, DRD4 7-repeat allele carriers were reported to display the highest level of impulsivity in adulthood when raised under low social economic conditions, and the lowest level of impulsivity when raised under high social economic conditions (Sweitzer et al., 2013). These 'for-better-and-forw worse' findings are supported by the observation that rodents lacking the DRD4 and modeling the DRD4 polymorphism (Grady et al., 2013) demonstrate both increased reward (Rubinstein et al., 1997) and stress sensitivity. In addition, trait SPS, which is chaterized by increased sensitivity to both negative and positive stimuli (Section 1), has been associated with a cumulation of dopamine-related genes (Chen et al., 2011; Weyn et al., 2022).

2.3. Brain-derived neurotrophic factor gene variance

Regarding neurotrophin signaling, the Brain Derived Neurotrophic Factor (BDNF) gene is of interest in the context of environmental sensivity (Belsky et al., 2022). Humans bear a polymorphism in the BDNF gene, the val/met polymorphism, of which the met allele is associated with impaired dendritic BDNF release (Chiaruttini et al., 2009). It has been demonstrated that BDNF met carriers compared to val allele carriers showed both the lowest level of reappraisal ability (i.e. the success of using reappraisal to downregulate negative affect) in childhood maltreated participants, and the highest level of reappraisal ability in non-maltreated participants (Miu et al., 2017). In line, a variant BDNF mouse (BDNFMet/Met) that reproduces the phenotypic hallmarks in humans with the variant BDNF met allele displayed increased anxiety-like behavior (Chen et al., 2006) and vulnerability to stress induced anxiety (Yu et al., 2012). The anxiety-like behavior in these mice could be rescued by exposure to music (Li et al., 2010). It has furthermore been reported that BDNF met allele carriers, compared to val allele carriers, demonstrated the lowest levels of indiscriminate social behavior after high quality foster care and the highest levels after care as usual conditions during childhood. These effects were strengthened if the children were also carrying the 5-HTTLPR s-allele (Drury et al., 2012). Likewise, carriers of both the BDNF met allele and 5-HTTLPR s-allele were found to interact with family environment quality to predict depression among males and females at age 15 in a for-better-and-for worse manner (Dalton et al., 2014). Other work demonstrated that both the 5-HTTLR s- and DRD4 7-repeat alleles strongly interact with the BDNF met allele in the response to the environment in children (Belsky et al., 2022; Zhang et al., 2021), suggesting that monoaminergic and neurotrophin genes combined amplify environmental sensitivity.

3. Sensitive periods: plasticity mechanisms

The behavioral plasticity associated with genes that increase environmental sensitivity (Section 2) is most likely related to neuroplasticity, a process through which the external and internal environment of an individual gradually becomes represented in neuronal structure and function during development and through experiences (Castren and Antila, 2017). Although gross connectivity develops through pre-programmed processes, fine-tuning takes place through experience-dependent plasticity. Experience-dependent developmental plasticity occurs during "critical periods" and "sensitive periods.'' Both terms refer to transient time windows characterized by heightened plasticity during which specific neural circuits undergo a change in response to environmental factors, affecting brain function. While the two terms are not seldom used in an interchangeable manner, they actually refer to somewhat different conditions. Indeed, it has been has been proposed that "critical periods'' differ from "sensitive periods'' based on dynamics (Knudsen, 2004). More specifically, "critical periods" are explained as acute shifts in plasticity during exclusive developmental timepoints, with a clear onset and offset (Hensch, 2005; Hubel and Wiesel, 1970). During these periods exposure to expected environmental experience takes place and neural networks develop into a configuration that is permanent. If changes in development in a specific brain region occur, these are irreversible. An example of this is ocular dominance in the visual cortex; only during the critical period ocular dominance columns are vulnerable to shrinkage (less and smaller cells) and responsive to visual stimuli to prevent this shrinkage (Hubel and Wiesel, 1970). Critical periods have also been observed for other sensory brain regions, as well as corticolimbic areas (Takesian and Hensch, 2013). Differently, "sensitive periods" can be explained as windows of opportunity for learning. During these periods experience can influence network configurations in various different ways and these conformations remain subjective to remodeling during a protracted period of brain development and adulthood. Accordingly, sensitive periods are associated with experience-dependent plasticity that is to some extent reversible and never fully close as critical periods do (Knudsen, 2004). Since increased environmental sensitivity is characterized by plasticity at young age as well as adulthood (see Section 2), but more so at young age (Belsky et al., 2009; Homberg and van den Hove, 2012), it can be hypothesized that increased environmental sensitivity is associated with sensitive period changes. In the next subsections we discuss the key plasticity mechanisms implicated in sensitive periods.

3.1. Maturation of GABAergic inhibitory neurons

Mechanistically, sensitive periods are thought to relate to changes in plasticity as observed during critical periods but without a definite closure. The main characteristic of critical periods involves the maturation of the GABAergic system, specifically parvalbumin (PV) positive GABAergic neurons (Hensch, 2005; Hensch et al., 1998; Huang et al., 1999). These fast-spiking cells extend lateral inhibition onto nearby pyramidal cells, influence action potential firing, and orchestrate rhythmic gamma oscillations. Maturation and maintenance of PV cells is very sensitive to experience. Without experience, the number and strength of PV synapses onto pyramidal cells is reduced and PV cell membrane properties remain immature (Reh et al., 2020). A critical period is initially characterized by reduced inhibitory PV interneuron input onto pyramidal cells, contributing to network disinhibition and an increased excitation-inhibition ratio in pyramidal neurons. The maturing inhibitory circuitry increasingly suppresses spontaneous, stimulus-irrelevant activity in favor of stimulus-driven inputs, increasing the signal-to-noise ratio of stimulus-evoked circuit activity (Toyoizumi et al., 2013). The closure of a critical period is marked by a fully matured GABAergic inhibitory network. Multisynaptic inhibition by developed PV interneurons restricts the summation window for spike time dependent plasticity, favoring the most temporally synchronous inputs, and facilitates NMDA-receptor dependent long-term potentiation (LTP) plasticity (Pouille and Scanziani, 2001). The onset and closure can be manipulated by pharmacological approaches that influence the inhibitory nature of the GABAergic/PV neurons, e.g. through benzodiazepine treatment or environmental enrichment, which fasten the onset of the criticial period (Fagiolini and Hensch, 2000), or e.g., dark rearing (in case of the development of the visual cortex) (Morales et al., 2002), reducing the sensory input needed for maturation and thereby delaying the onset of the critical period.

In the barrel cortex inhibitory circuits undergo activity-dependent changes during the early postnatal period. Chronic whisker deprivation decreases inhibition of pyramidal cells mediated by PV interneurons. By varing the time of whisker removal and studying effects on activity-dependent regulation of PV interneuron circuits, it was found that the critical period for this plasticity spans P0–14 (Lo et al., 2017). In

line, electrophysiological and chemical properties of PV cells in the layer 4 barrel cortex reach nearly adult levels around the second postnatal week. These properties of PV cells were found to be delayed in the absence of BDNF while BDNF promoted the development of dendritic arborization of pyramidal cells (Itami et al., 2007). The PV neurons surround glutamatergic synapses (Minlebaev et al., 2007) which produce spindle-bursts that are required for normal development of receptive fields in barrel neurons (Fox et al., 1996). LTP mediated by these glutamatergic synapses at the thalamocortical synapses of the barrel cortex is confined to the first postnatal week, but not restricted to the critical period (Crair and Malenka, 1995). Thalamocortical synapses also express long-term depression (LTD) during development (Feldman et al., 1998). Both forms of synaptic plasticity may contribute to plasticity during the sensitive period.

In the prefrontal cortex, GABAergic inhibitory circuitry modifications are observed during adolescence, according to the idea that critical periods progress in a hierarchical fashion, starting from primary sensory areas and progressing to areas of cortex involved in higher-order processing necessary for more complex cognition and experience (Takesian and Hensch, 2013; Toyoizumi et al., 2013). PV proteins levels and number of PV positive interneurons are higher in the adolescent (P45–55) rat medial prefrontal cortex than in that of juvenile (P25–35) animals (Caballero et al., 2014). Likewise, in the dorsal lateral prefrontal cortex of non-human primates, PV expression and PV axon terminals increase during the pubertal period (Erickson and Lewis, 2002; Hoftman and Lewis, 2011; Hoftman et al., 2015). At the same time, inhibitory neurotransmision increases in both mice and non-human primates (Gonzalez-Burgos et al., 2015; Piekarski et al., 2017). Computational simulations indicate that these developmental changes should lead to mature gamma oscillatory capability in PFC (Gonzalez-Burgos et al., 2015). It was found that maternal separation between PND2–20 caused a reduction in the expression of PV gene expression at PND35 in the prefrontal cortex, and that this could bye rescued by environmental enrichment from PND21 (Irie et al., 2023). These results suggest that an early adverse environment disturbs the development of the mPFC but that these abnormalities allow room for recovery depending on the subsequent environment. A recent study provided further causal evidence that PV neuron activity is implicated in the sensitive period in the prefrontal cortex. More specifically, it was shown that decreasing medial prefrontal cortex PV interneuron activity during juvenile and adolescent development (P14–50) through chemogenetics produced persistent impairments in adult cognitive flexibility with corresponding deficits in PV interneuron-pyramidal cell functional connectivity and task-evoked gamma oscillations (Canetta et al., 2022). In contrast, chemogenetic suppression of PV interneuron activity in adulthood produced no lasting effects (Canetta et al., 2022), supporting that P14–50 reflects a sensitive period for the prefrontal cortex. These findings show that abnormal PV interneuron activity during a region's sensitive period alters adult prefrontal circuit function and cognitive behavior.

3.2. BDNF signaling

The role of BDNF in brain development has been widely demonstrated (Kowianski et al., 2018). Depending on the cell type, BDNF can be release in a constitutive or activity-dependent manner (Mowla et al., 2001) and the ratio between the two forms of the BDNF proteins (pro and mature) can change according to particular stages of brain development (Kowianski et al., 2018). The fundamental process determining the effect of BDNF after the binding with the TrkB receptor complex involves the translocation of the complex towards cellular membrane lipid rafts (Suzuki et al., 2004). Interestingly, both the expression of BDNF and the TrkB receptor are developmentally regulated according to a time-course that parallels critical periods (Allendoerfer et al., 1994; Castren et al., 1992; Schoups et al., 1995). On these bases, already more than 30 years ago it was suggested that neurotrophins can influence neuronal survival and differentiation in an activity-dependent fashion (Bonhoeffer, 1996). For instance, BDNF synthesis in the visual cortex is regulated by visual stimulation (Castren et al., 1992). In line, it has been demonstrated that BDNF is a key regulator of GABAergic plasticity and influences the opening of critical periods during postnatal development by steering the maturation of the GABAergic system (Hensch, 2005; Hensch et al., 1998; Huang et al., 1999; Mizuno et al., 1994). Furthermore, brief interference with depolarizing GABA during early development was found to prolong critical-period plasticity in visual cortical circuits, that this effect was accompanied by dampened inhibitory neurotransmission and downregulation of BDNF expression, and that a pharmacological increase of BDNF signaling during GABA interference rescued the effects on plasticity and its regulators later in life (Deidda et al., 2015). Moreover, BDNF over-expression shifts the onset and closure of the critical period to the left in time (i.e. earlier in development) (Sale et al., 2010), and BDNF blockade inhibits critical period plasticity in the primary visual cortex (Hanover et al., 1999; Huang et al., 1999). It has been reported that during P28 to P33/34 in the visual cortex there is a transient period of synaptic and neurochemical imbalance, that this goes along with a decrease in the expression of BDNF and TrkB receptors, and that in vivo TrkB agonist treatment partially reversed the synaptic imbalance in normal and monocularly-deprived neurons during this time (Zhang et al., 2018). Finally, both BDNF expression and GABA transmission are reduced in sensory deprivation experiments that delay critical period onset (Morales et al., 2002). Thus, BDNF may be a mechanistic link between stimulus-evoked activity and the maturation of GABAergic inhibitory circuitry during critical period development (Deidda et al., 2015). In the next section we will discuss how serotonin and dopamine influence GABA and BDNF related processes during sensitive periods.

4. Serotonergic and dopaminergic modulation of plasticity during sensitive periods

4.1. Serotonin

There are several lines of evidence indicating that serotonin interferes with plasticity mechanisms during sensitive periods. Early studies demonstrated that 5-HT has the capacity to promote cortical plasticity demonstrated during the critical period of ocular dominance plasticity in kittens (P20–P40). During this phase transient changes in regional and columnar specific organization of 5-HT2 receptors were found, which were dependent on sensory visual inputs (Dyck and Cynader, 1993). It was furthermore found that 5-HT2C antagonists reduced OD plasticity (Gu and Singer, 1995; Wang et al., 1997). Subsequent studies showed that serotonin directly affects LTP and LTD in the visual cortex during the critical period (Edagawa et al., 2001; Kojic et al., 1997). More specifically, in visual cortical slices, taken from 40-day-old kittens, bath application of serotonin facilitated the induction of both LTD and LTP. No such serotonin facilitation of long-term plasticity was detected in $>$ 120-day-old animals, indicating that serotonin facilitates synaptic plasticity within a defined period of visual cortical development (Kojic et al., 1997). Furthermore, it has been found that the induction of LTP is inhibited by the addition of exogenous serotonin in slices from 3-week-old rats, while a seronergic lesion enhanced LTP in 5-week old rats (Edagawa et al., 2001). Another study reported that postnatal serotonin depletion by para-chlorophenylalanine between P10–20 decreased BDNF mRNA expression in the hippocampus of rats, which was rescued by environmental enrichment (Saadati et al., 2023), a factor that is known to fasten the onset of the critical period (Fagiolini and Hensch, 2000). Furthermore, in vivo electrophysiological studies in rat pups revealed that selective serotonin reuptake inhibitor (SSRI) exposure between P2–5, but not between P21–29, resulted in a rapid suppression of spontaneous cortical activity in the somatosensory cortex and inhibition of sensory-evoked oscillatory bursts (Akhmetshina et al., 2016). Towards the closing of critical/sensitive periods, it was found that SSRI treatment from P2 to P21 evoked a robust reduction in

perineural nets deposited around PV interneurons in hippocampal subregions at P21 (Mukhopadhyay et al., 2021). Likewise, another study found that exposure to an SSRI from gestational day 7 until postnatal day 7 did not affect the number of PV cells and PV intensity but decreased perineural net formation around the cells at P17 (ongoing critical period) and P24 (closure critical period)) in the amygdala and hippocampus (Fretham et al., 2012; Umemori et al., 2015). These findings suggest that perinatal / early postnatal SSRI exposure might delay the closure of the critical periods in the amygdala and hippocampus (Umemori et al., 2015). The finding that intraperitoneal administration of MDMA reopened the social reward behavior critical period by binding to the 5-HTT and triggering LTD at excitatory synapses (Nardou et al., 2019) further suggests the implication of serotonin in the reopening of critical/sensitive periods. It is possible that serotonin maintains plasticity after the critical period. This idea is supported by the finding that visual deprivation at P21–23, after the closure of the critical period of the visual cortex, increases extracellular serotonin in the juvenile rat barrel cortex and in turn facilitates synaptic strengthening within the barrel cortex (Jitsuki et al., 2011).

4.2. Dopamine

Regarding dopamine, there is evidence that dopamine accelerates the development of frontal PV neurons both in vitro and ex vivo through interactions with dopamine D2 (Porter et al., 1999). In vitro it was found that dopamine accelerated PV expression in organotypic slices of rat frontoparietal cortex (Porter et al., 1999). Treatment with a dopamine D1 receptor agonist had little effect, whereas a dopamine D2 agonist mimicked dopamine's effects. Likewise, the dopamine D2 but not the dopamine D1 antagonist blocked dopamine-induced changes, indicating that they were mediated primarily by dopamine D2 receptors. Ex vivo, in prepubertal rodents, patch clamp recordings of PFC slices demonstrated that dopamine can excite PV interneurons via D1 receptors, and that during adolescence dopamine further excites these cells via dopamine D2 receptors (Tseng and O'Donnell, 2007), causing greater inhibitory activity in response to dopamine release throughout adolescence and adulthood. This developmental change allows dopamine to facilitate inhibitory circuit function, including noise suppression by increasing the synchrony of gamma oscillations (Cardin et al., 2009; Doischer et al., 2008) and decreasing the excitation/inhibition balance (O'Donnell, 2010).

In summary, both serotonin and dopamine can influence sensitive period plasticity mechanisms, providing a potential mechanism through which the genetic factors that increase environmental sensitivity (Section 2) could affect sensitive periods. To further support this idea, we describe in the next section how serotonin and dopamine and these genetic factors influence brain development.

5. Serotonin, dopamine and brain development

While sensitive periods are preprogrammed phases in development, it is likely that they are subject to individual differences in brain development shaped by genetic and environmental factors. This reasoning is based on the fact that serotonin and dopamine, and genetic factors that shape individual differences in behavior and influence serotonin signaling, influence brain development, including the formation of barrel cortex and visual maps (Gaspar et al., 2003; Homberg et al., 2010; Money and Stanwood, 2013). Hence, the genetic factors that increase environmental sensitivity and affect serotonin and dopamine signaling have the potential to alter brain development with long-lasting effects, including the timing of and/or plasticity during sensitive periods. In the subsections below we describe how serotonin and dopamine affect brain development, with effects that converge on sensitive period processes.

5.1. Serotonin

Regarding serotonin, it has been established that in mice, serotonergic neurons expressing the serotonergic synthesis machinery as well as the 5-HTT are born at embryonic day (E) 10.5 in the raphe nuclei, which reach the forebrain around E17.5 (Bonnin et al., 2011; Garcia et al., 2019). At this developmental stage, serotonin decreases GABAergic interneuron as well as glutamatergic pyramidal neuron migration in a reversible and dose-dependent manner (Riccio et al., 2011, 2009). Accordingly, an excess of 5-HT during development due to the 5-HTT genotype is associated with an impairment in the positioning of cortical interneurons (Riccio et al., 2011, 2009) (at birth) as well as pyramidal neurons (at E19). These 5-HTT genotype-driven changes have the strong potential to affect PV neuron maturation during sensitive periods. In addition, soon after the birth of the serotonergic neurons, 5-HTT expression extends to non-serotonergic neurons, including the glutamatergic principal projection neurons of the sensory systems (thalamus, retina, somatosensory cortex), the corticolimbic pathways (hippocampus (E14-E15), and the prefrontal/cingulate cortex (E17.5). 5-HTT expression in non-serotonergic neurons ends rapidly during the second postnatal week (Gaspar et al., 2003; Lebrand et al., 1996, 1998; Salichon et al., 2001). This ectopic expression of the 5-HTT has also been obserbed in human embryos (Verney et al., 2002). These neurons are referred to as serotonin-absorbing neurons (Jafari et al., 2011). Their expression coincidences with serotonin levels which peak within the first postnatal week, after which they decline, reaching adult levels at around postnatal day (P) 15 (Hohmann et al., 1988). Transient expression of the 5-HTT has been suspected to play a role in barrel cortex and visual map development (Gaspar et al., 2003; Homberg et al., 2010) and provides another mechanism via which 5-HTT genotype can influence sensitive periods. In support, deletion of 5-HTT expression on thalamocortical projection neurons projecting to the somatosensory cortex, specifically the barrel cortex representing the whiskers, leads to changes in thalamocortical axon patterning and intracortical dendritic arborization, with dendritic segments in neighboring columns that remain into adulthood (Chen et al., 2015). Such effects are not observed after depletion of the 5-HTT in the raphe nuclei (Chen et al., 2015). In addition, it was found that compared to the wild-type condition, 5-HTT knockout altered local cerebral glucose utilization (a measure of brain activity) in the somatosensory cortex in adulthood in response to whisker stimulation, and that this could be rescued by lowering serotonin levels by administration of the selective tryptophan hydroxylase inhibitor p-chlorophenylalanine between P0 and P1 (Esaki et al., 2005). Administration of p-chlorophenylalanine at later timepoints, up to P5, also rescued the abnormal barrel patterns in 5-HTT knockout mice, but with progressively less efficacy (Persico et al., 2001), suggesting that the effect of 5-HTT knockout on somatosensory cortex function in adulthood is mostly dependent on sensivity to serotonin during early postnatal development of this region. This has long-lasting effects on neuronal network function in the cortex and sensory processing (Van der Knaap et al., 2021).

Inherited 5-HTT down-regulation affects both serotonin levels during early brain development, when serotonin mostly exerts neurotrophic actions, and serotonin levels during later life, when serotonin acts as neurotransmitter. This makes it hard to discern to what extent effects of 5-HTT down-regulation have a developmental origin and interfere with sensitive periods. Of interest, there is strong evidence that transient pharmacological 5-HTT blockade during the perinatal / early postnatal phase induces effects that resemble those associated with 5-HTT knockout. Thus, early postnatal SSRI treatment (P0-P6) and 5-HTT knockout, each compared to their respective vehicle treated and wild-type controls, similarly affect barrel cortex anatomy; treated and knockout rats show a more diffuse barrel pattern and thinned out but wider terminal clusters of thalamocortocal afferents in layer IV (Lee, 2009), which is still observed in preadolescence (for review see: (Homberg et al., 2010). At the behavioral level, SSRI administration

between gestational day 11-P7 leads to a delay in motor and reflex development lasting up to weaning (P21) as was also observed in 5-HTT knockout rats (Kroeze et al., 2016). Furthermore, SSRI exposure during P4-P21 leads to anxiety- and depression-like behavior is adulthood, similar to behavior characteristic for adult 5-HTT knockout mice (Ansorge et al., 2004). These findings suggest that phenotypes observed in association with inherited 5-HTT down-regulation are -at least in part- due to serotonin-mediated changes in brain development and -given the effects of serotonin on sensitive periods (Section 4) - also serotonin-mediated interference with sensitive periods.

5.2. Dopamine

Dopamine also affects brain development, but according to a different pattern. The development of cortical dopamine innervation starts during the embryonic period and continues to increase until P60, after which density and topography of DAergic afferents remain constant (Islam et al., 2021). Several measures of dopaminergic system maturation transiently peak during adolescence. For example, dopamine receptors are first expressed at the embryonic stage and during postnatal development, and continue to gradually increase until P28–P40, after which it diminishes again to reach stable levels at around P60 (for review see: (Islam et al., 2021; Suri et al., 2015)). Hence, dopamine system maturation follows an expansion–contraction course, peaking during late adolescence. In line, the developmental period sensitive to dopaminergic manipulations falls between P22–41 (Suri et al., 2015). How DRD4 genotype would influence brain development has, to the best of our knowledge, not been studied so far. Yet, of interest is that the embryonic development of the dopaminergic system, the outgrowth of midbrain dopamine neurons to the prefrontal cortex, is influenced by the serotonergic system (Garcia et al., 2019).

In the next section we address changes in sensitive period markers in genetic animal models for increased environmental sensitivity.

6. Sensitive period plasticity changes in animal models mimicking genetic variations associated with increased environmental sensitivity

6.1. Serotonin transporter knockout rodents

The animal models that have been most extensively investigated in relation to plasticity mechanisms are 5-HTT knockout mice and rats, mimicking the 5-HTTLPR s-allele (Caspi et al., 2010a; Schipper et al., 2019). These animals exhibit increased extracellular serotonin levels compared to wild-type controls throughout life, in the absence of changes in the catecholamine systems (Homberg et al., 2007; Mathews et al., 2004; Verheij et al., 2014). The observation that key phenotypes of 5-HTT knockout mice and rats, such as increased anxiety and changes in sensory processing, can be mimicked by early postnatal SRRI treatment (Ansorge et al., 2004; Homberg et al., 2010; Kroeze et al., 2016) (see Section 5) suggests that the increased environmental sensitivity displayed by these animals relate to changes in brain development, including sensitive periods. Because serotonin has a strong influence on the development of the somatosensory cortex, specifically the barrel cortex representing the whiskers, the barrel cortex has been mostly studied in these models. A key finding is that at P21, feedforward inhibition of pyramidal neurons is decreased in the somatosensory cortex of 5-HTT knockout rats versus wild-type controls (Miceli et al., 2017). In addition, the number of GABAergic puncta on pyramidal neurons is decreased (Miceli et al., 2017), suggesting that reduced feed-forward inhibition is due to decreased inhibitory input onto the excitatory pyramidal neurons. This may increase the time window for temporally relevant information to be integrated before the inhibitory input shunts any latent response (Miller et al., 2001; Swadlow, 2003). At the neural population level excitatory signal propagation is increased in the somatosensory cortex (Miceli et al., 2017), indicating that the excitatory/inhibitory balance has shifted to excitation. These findings together suggest that lifelong increased serotonin levels due to inherited 5-HTT down-regulation delays the sensitive period in the somatosensory cortex. 5-HTT knockout has also been shown to alter the topological organization of thalamocortical axons targeting in the barrel cortex at P21. In 5-HTT knockout rats, compared to wild-type controls, these axonal projections have lost their predominant one-to-one association to the individual home column. The axonal projections are also less arborized and possess fewer boutons (Miceli et al., 2013). This loss in topographic precision found could result in a reduced transmission efficiency of tactile sensory signals from the thalamus to the barrel cortex. Furthermore, the topographic changes may extend to adulthood, as we found that 5-HTT knockout is associated with smaller barrels and space between barrels at postnatal day 21 (Miceli et al., 2013) and in adulthood (Miceli, Schubert, Homberg, unpublished data). In line, Chen et al. (Chen et al., 2015) reported that barrel cortex map formation in mice with the 5-HTT deleted from thalamocortical neurons during the sensitive period for this region was still disrupted at 6 weeks of age compared to controls. The topological changes are characteristic of increased immaturity (Miceli et al., 2013) and may add to the idea that there is a delay and extension in the sensitive period of the barrel cortex in 5-HTT knockout animals.

Besides the barrel cortex, in the prefrontal cortex, the expression of various GABAergic markers, including glutamic acid decarboxylase-67 (Gad67), gamma 2 (GABA(A)-γ2) and PV, was found to be decreased in juvenile and adolescent (Calabrese et al., 2013; Guidotti et al., 2012) as well as adult 5-HTT knockout compared to wild-type rats (Guidotti et al., 2012; Sbrini et al., 2020), and in perinatally SSRI rats (Guidotti et al., 2012). In the amygdala, a significant reduction of amplitude and frequency of spontaneous compound inhibitory postsynaptic currents (IPSCs) was found in adult 5-HTT knockout rats compared to wild-type controls (Johnson et al., 2019). Furthermore, we recently found that gamma osccilation synchronization between the amygdala and orbitofrontal cortex are strongly reduced in adult 5-HTT knockout versus wild-type rats performing a basic auditory discrimination task, indicative for immaturity of the inhibitory circuitry in corticolimic areas (Boillot et al., submitted). It is possible that the major change in gamma band osscilations in adulthood emerge from serotonin interference with the prefrontal cortex sensitive period previously identified by Canetta et al. (2022)(see Section 3). Because the immaturity is observed in adulthood and the animals show normal reinforcement learning, it is well -again- possible that the sensitive period is maintained and extended.

5-HTT knockout, compared to the wild-type condition, has also been associated with reduced gene expression of the transcription factor BDNF and of Npas4 in the prefrontal cortex from P7 and 14, respectively, until adulthood (Guidotti et al., 2012;Calabrese et al., 2013). A decrease in BDNF, regulated by Npas4, may be a driving force behind the delayed development of the inhibitory networks in 5-HTT knockout rats (Hong et al., 2008; Spiegel et al., 2014), in line with the finding that a decrease in BDNF levels delays the onset of the critical period (see Section 3) and that *NPAS4* down-regulation prevents ocular dominance plasticity induced by adult fluoxetine exposure (Maya-Vetencourt et al., 2012). Npas4 is an activity-regulated transcription factor, whose neuronal expression is selectively induced by Ca^{2+} influx and has a critical role in the development of inhibitory synapses by regulating the expression of activity-dependent genes (Lin et al., 2008). Npas4 is a transcription factor that binds to promoters I and IV of the *Bdnf* gene to regulate its expression, suggesting that it may directly regulate activity-dependent expression of the neurotrophin (Lin et al., 2008). As 5-HTT knockout rats have reduced *Bdnf* gene expression in the prefrontal cortex, from P7 (Calabrese et al., 2013) up to adulthood (Luoni et al., 2013), and that this occurs through the modulation of different *Bdnf* transcripts, including exon I and exon IV (Molteni et al., 2010), the delay but extension of cortical GABAergic circuit maturation maybe due to a reduction in BDNF levels. The finding that lenti-viral mediatied

upregulation of BDNF in the hippocampus is able to rescue anxiety-like phenotypes in 5-HTT knockout rats (Diniz et al., 2021) suggests that normalization of BDNF levels is able to reduce the environmental sensitivity in these animals.

The decrease in BDNF levels could have an epigenetic cause, given that *Bdnf* gene promotor IV methylation is significantly increased in the prefrontal cortex of 5-HTT knockout rats during pre-adolescence, adolescence and in adulthood. This is paralleled by a decrease in growth arrest and DNA-damage-inducible beta (*Gadd45β*) gene expression (Calabrese et al., 2013), which is involved in DNA demethylation of the *Bdnf* promoter, and an increase in DNA (cytosine-5)-methyltransferase 1 (Dnmt1) gene expression (Calabrese et al., 2013).

Importantly, the effects of 5-HTT knockout on reduced *Npas4, Gad67, GABA(A)-γ2, PV* and *Bdnf* gene expression levels in the hippocampus and prefrontal cortex could be rescued by treatment with the selective serotonin and norepinephrine reuptake inhibitor duloxetine in adulthood (Guidotti et al., 2012). Likewise, the serotonergic and dopaminergic drug lurasidone was able to rescue the reduced *Npas4,* PV, *GABA(A)-γ2,* and Bndf in 5-HTT knockout rats along with their impaired fear extinction (Luoni et al., 2013). We also found that enriched housing in adulthood normalized both the anxiety- and depression-related behaviors seen in 5-HTT knockout versus wild-type rats rats and the reduced levels of BDNF, Gad67, $GABA_A\gamma 2$, and *PV* in these animals (Sbrini et al., 2020). These data indicate that the molecular changes associated with sensitive periods are correlated and reversible and that the neuroplastic condition is dynamic and experience-dependent, akin a sensitive period that never fully closes (see Section 3). In summary, inherited 5-HTT down-regulation may delay but extend sensitive periods.

6.2. Dopamine D4 receptor knockout rodents

Also in DRD4 knockout animals plasticity mechanisms have been studied. Given that DRD4 is found on both PV interneurons and excitatory neurons, in sensory, prefrontal cortex and limbic regions (Cousineau et al., 2020; Furth et al., 2013; Graham et al., 2015; Potts and Bekkers, 2022; Zhong and Yan, 2016), the dopamine system may well influence the timing of and/or plasticity during sensitive periods. Because the DRD4 7-repeat allele is associated with DRD4 down-regulation (Schoots and Van Tol, 2003; Simpson et al., 2010; Thompson et al., 1997; Van Tol et al., 1992; Zhong and Yan, 2016), DRD4 knockout animals are useful to explore the potential neuroplasticity changes associated with these polymorphisms. In general, work with DRD4 knockout mice, compared to wild-type controls, revealed decreases in cortical inhibition (Tan et al., 2019) and increases in (sub)cortical excitability in adulthood (Cepeda et al., 2001; Rubinstein et al., 2001; Thomas et al., 2009). More specifically, it was found that exposing DRD4 knockout mice to one week of restraint stress induced significant deficits in sensorimotor gating, and reduced GABAergic transmission in the prefrontal cortex. Administration of diazepam, a GABA enhancer, restored GABAergic synaptic responses and ameliorated some behavioral abnormalities in stressed DRD4 knockout mice (Tan et al., 2019). It has also been reported that the frequency of spontaneous synaptic activity was increased in cortical pyramidal neurons of DRD4 knockout versus wild-type mice (Rubinstein et al., 2001), indicative for hyperexcitability. Furthermore, resting extracellular levels of glutamate are increased in the striatum of DRD4 knockout mice (Thomas et al., 2009). These data imply that in adult DRD4 knockout mice, inhibition is reduced and excitation is increased, which could point to an extended sensitive period of the cortex in adulthood.

6.3. BDNF knockout rodents

In heterozygous BDNF knockout juvenile mice, compared to wild-type controls, ex vivo electrophysiological recordings revealed a decreased frequency and amplitude of miniature inhibitory postsynaptic currents (mIPSCs) as well as a reduced amplitude and prolonged decay time constant of evoked IPSCs. Further analyses indicated an impaired presynaptic GABAergic function in these mice, as shown by a decreased release probability, steady-state release, and synchronous release of GABA. Additionally, the overall balance in the strength of cortical excitation to inhibition shifted towards decreased inhibition (Abidin et al., 2008). These findings suggest that chronically reduced levels of BDNF strongly impair the GABAergic inhibitory function in the visual cortex by altering postsynaptic properties and reducing presynaptic GABA release as well as the overall strength of inhibition onto pyramidal neurons within the cortical network. In line, an in vitro study revealed that the number of GABAergic terminals on the soma of BDNF knock-out neurons was smaller than that of neighboring control neurons and that the frequency of mIPSCs of BDNF knockout neurons was lower than that of control neurons (Kohara et al., 2007). Furthermore, regarding the barrel cortex, it has been reported that barrel patterns form but thalamocortical patterning is delayed in BDNF knockout mice (Lush et al., 2005). These impairments of inhibitory function and thalamocortical patterning are compatible with an immature status of the GABAergic system in heterozygous BDNF mice, which supports the hypothesis that the level of BDNF expression delays the onset of the sensitive period and the maturation and function of the GABAergic system (Abidin et al., 2008) (see Section 3).

6.4. Summary

Taken together, the 5-HTT, DRD4 and BDNF knockout animal models have in common that they exhibit a decrease in (sub)cortical inhibition, leading to increased neuronal excitability While 5-HTT knockout seems to both delay and extend the sensitive period, BDNF knockout may delay the onset of the sensitive period, and DRD4 knockout may extend the sensitive period (Fig. 1). It is furthermore conceivable that increased environmental sensivity driven by these genetic factors itself influences the onset and duration of the experience-dependent sensitive periods (for further discussion see Section 9).

7. Sensory processing changes in animal models mimicking genetic variations associated with increased environmental sensitivity

7.1. Serotonin transporter knockout rodents

Changes in the timing of and plasticity during sensitive periods in highly sensitive individuals likely affects sensory processing (i.e. the processing of environmental stimuli) and various behavioral manifestations. More specifically, reduced cortical inhibition as found in 5-HTT knockout animals (Section 6) is expected to allow more latent information to enter perception, there enabling the observation of stimuli that the brain of others (being less sensitive or less open) would block out. As such, juvenile 5-HTT knockout rats, compared to wild-type controls, show faster sensory integration in the gap crossing task (Miceli et al., 2017). In addition, it was found that both 5-HTT knockout rats and rats exposed to SSRI treatment between P1-P7, compared to their respective controls, needed less whisker touches to the decision to cross the gap (Azarfar et al., 2019). Computational modeling revealed that both models were lacking adaptive sensorimotor control as normally seen in adult rats. Thus, while adult rats decrease whisk amplitude as they get closer to the target, the whisking amplitude remained high in the 5-HTT knockout and early postnatal SSRI exposed rats. As a consequence, these animals were including more information in their perceptual actions, and while this is more costly, it did allow the animals to make the gap crossing decision faster. The phenotypic similarity between the 5-HTT knockout and postnatal SSRI exposed rats suggests that the phenotype of the 5-HTT knockout rats relates to serotonergic interference with the sensitive period of the barrel cortex. Along the same vein, it was found that 5-HTT rats compared to wild-type controls

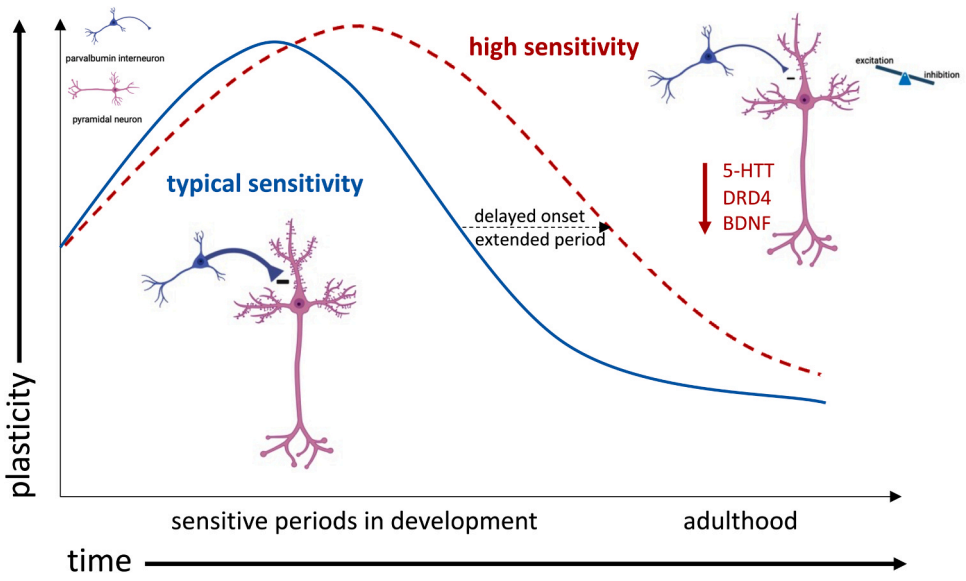

Fig. 1. Hypothetical schematic of plasticity and cellular changes in subjects with high environmental sensitivity. The hypothesis is that the onset of sensitive periods is delayed and/or that their duration is extended in sensory and limbic brain regions. The inhibition of 5-HTT, DRD4 and BDNF causes an unbalance between excitation and inhibition thus leading to heightened plasticity and increased environmental sensitivity throughout life. BDNF = Brain Derived Neurotrophic Factor; 5-HTT = serotonin transporter; DRD4 = dopamine D4 receptor.

display reduced latent inhibition in adulthood (Nonkes et al., 2012b). Thus, the animals lack the typical retardation in conditioning following nonreinforced preexposure to a stimulus, suggesting that they ignore irrelevant information less compared to wild-type control animals. The animals show normal reward-based operant learning, but are more flexible in response to a reversal of cue-reward associations (Nonkes et al., 2013), and exhibit reduced goal-directed behavior when the reward is devaluated (Nonkes et al., 2010). Moreover, 5-HTT knockout rats show a lower learning rate and apply more of an exploitation versus exploration strategy compared to wild-type rats during category learning, as tested in a touchscreen operant box employing Gabor patches as stimuli. The decision bound of decision-making during stimulus generalization indicates that more 5-HTT knockout rats than wild-type rats exploit irrelevant information to categorize stimuli (Guo CC and Homberg, 2020). The slower learning rate naturally follows from the decreased fidelity of sensory data, as the creature cannot properly update its own beliefs. Finally, fear extinction learning and recall are slower in 5-HTT knockout rats (Nonkes et al., 2012a; Schipper et al., 2019; Shan et al., 2018), which may be attributed to the same mechanistic principle. Overall, the data suggest that increased environmental sensitivity in the 5-HTT knockout model relates to reduced filtering or blockade of irrelevant information, resulting in a perceptual system that 'keeps all options open'.

7.2. Dopamine D4 receptor knockout rodents

Increased excitation is furthermore expected to lead to lower threshold to perceive and respond to environmental stimuli, as may be seen in DRD4 knockout rodents. Indeed, compared to wild-type controls they are supersensitive to the locomotor stimulating effects of (met) amphetamine (Kruzich et al., 2004; Rubinstein et al., 1997), ethanol and cocaine (Rubinstein et al., 1997) and more responsive to stress (Falzone et al., 2002; Knop et al., 2020). The animals furthermore show low levels of exploration in novel situations (Dulawa et al., 1999). In approach/-avoidance conflict paradigms, DRD4 knockout mice, compared to wild-type controls, are more hesitant to travel into an open arm of a maze or lighted area in comparison to their wild-type counterparts (Falzone et al., 2002). Furthermore, they display differential susceptibility for the effects of early life experiences on licking/grooming levels in female mice; limited nesting and bedding reared heterozygous DRD4 knockout mice exhibited the lowest and communal nesting reared heterozygous DRD4 knockout mice exhibited the highest levels of licking/grooming (Knop et al., 2020). This behavioral pattern is also indicative for increased environmental sensitivity.

7.3. BDNF knockout rodents

Despite the key role of BDNF in the onset of critical/sensitive periods, rodents exhibiting a reduction in BDNF levels have normal visual and auditory sensory processing. However, compared to wild-type controls they do show a reduction in nociceptive and olfactory processing (Bath et al., 2008; MacQueen et al., 2001). Furthermore, they show increased anxiety (Chen et al., 2006). A variant BDNF mouse (BDNFMet/Met) that reproduces the phenotypic hallmarks in humans with the variant BDNF met allele displayed increased anxiety-like behavior (Chen et al., 2006) and vulnerability to stress induced anxiety (Yu et al., 2012). The anxiety-like behavior in these mice could be rescued by exposure to music (Li et al., 2010). This implies sensitivity to both negative and positive environmental stimulation, akin the environmental sensitivity concept.

7.4. Summary

In summary, 5-HTT, DRD4 and BDNF (heterozygous) knockout animal models display increased sensitivity and responsivity to sensory stimulation as well as negative and positive stimuli. 5-HTT knockouts may have a broader perceptual reach compared to controls and thereby include initially irrelevant information in perceptual events. This could be driven by reduced feed-forward inhibition of excitatory neurons, increasing the time span for additional stimuli to be included in the perceptual events. While this may require more efforts and slow down sensory-based decision making, it also fosters flexibility when environmental stimuli change. The behavioral responses of DRD4 knockout models may be driven by a lower threshold to perceive and respond to environmental stimuli, due to increased neuronal excitability per se. And BDNF knockout models may process environmental stimuli differently due to reduced inhibitory function, potentially in a similar manner as in 5-HTT knockout models (Fig. 2). Future research is required to

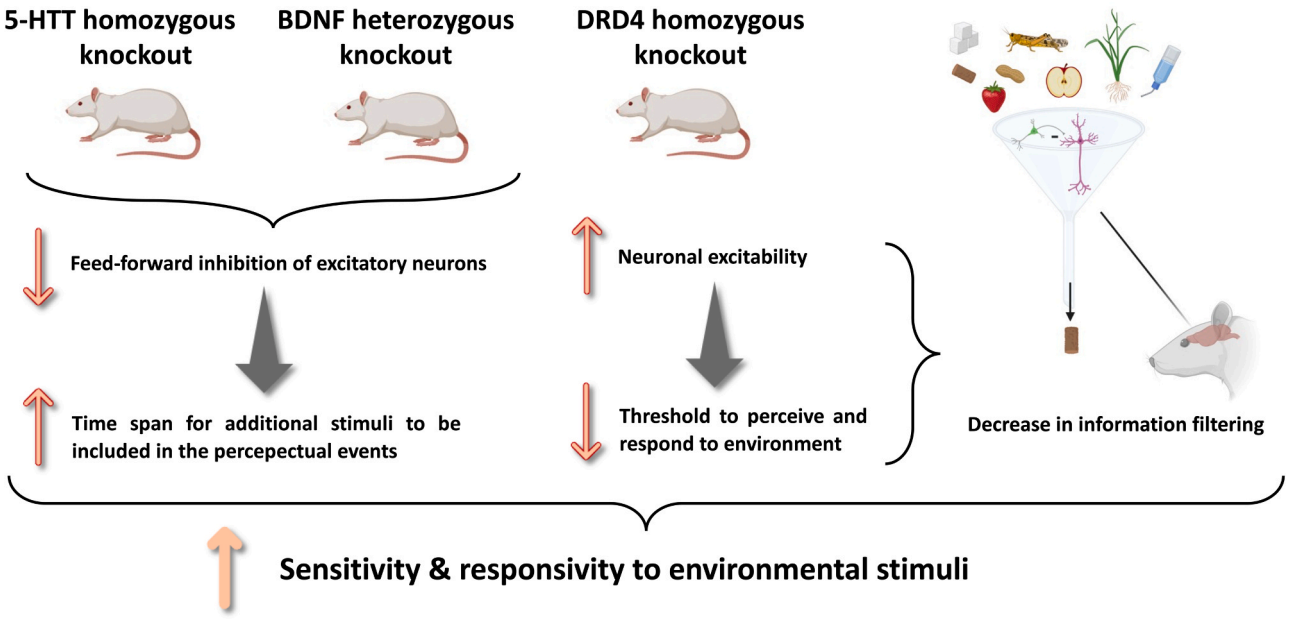

Fig. 2. . 5-HTT, DRD4 and BDNF knockout models show increased sensitivity and responsiveness when exposed to stimuli. The mechanisms underlying this difference may involve imbalances between excitatory/inhibitory transmission, leading to a decrease in information filtering. BDNF = Brain Derived Neurotrophic Factor; 5-HTT = serotonin transporter; DRD4 = dopamine D4 receptor.

further delineate how the monoamine and plasticity genes precisely affect sensory processing.

8. From local micro circuitries in animals to large-scale networks in humans

8.1. Sensory processing sensivity

While plasticity markers and microcircuitry function can be well studied in animal models (Section 6), they cannot be investigated in humans because of the inaccessibility of the brain. To connect to human research, understanding needs to be extended to the investigation of structural and functional changes in the brain as can be interrogated through non-invasive neuroimaging techniques like functional structural magnetic resonance imaging (MRI) and electroencephalography (EEG) (Fig. 3). In humans, the neural mechanisms associated with individual differences in SPS (see section 'environmental sensitivity') have been examined in a few studies. The level of SPS is determined by questionnaires (the Highly Sensitive Child Scale (Pluess et al., 2018) or the Highly Sensitive Person Scale for adults (Aron and Aron, 1997)) and typically the people with the extreme scores at the high and low SPS side are being compared. As such, high SPS has been associated with structural differences in primary sensory cortical regions (somatosensory cortex, auditory cortex), the dorsal and ventral visual pathways, and the prefrontal cortex (David et al., 2022) as well as significantly greater activation in brain areas involved in higher order visual processing and attention (Jagiellowicz et al., 2011). A recent study applied EEG under resting state conditions, and found increased higher absolute power in delta, theta, alpha, and beta frequency bands in persons scoring high in SPS, pointing to higher activity of cortical pyramidal cells at rest (Dimulescu C and Godde, 2020). Another recent study demonstrated that in response to a touch of an experimenter's hand, the brain of highy sensitive persons did not show differences in the activity of the somatosensory cortex, but showed increased activity in the insula, which is implicated in the integration of sensory information and awareness of it (Schaefer et al., 2022). This supports the idea that the brain of highly

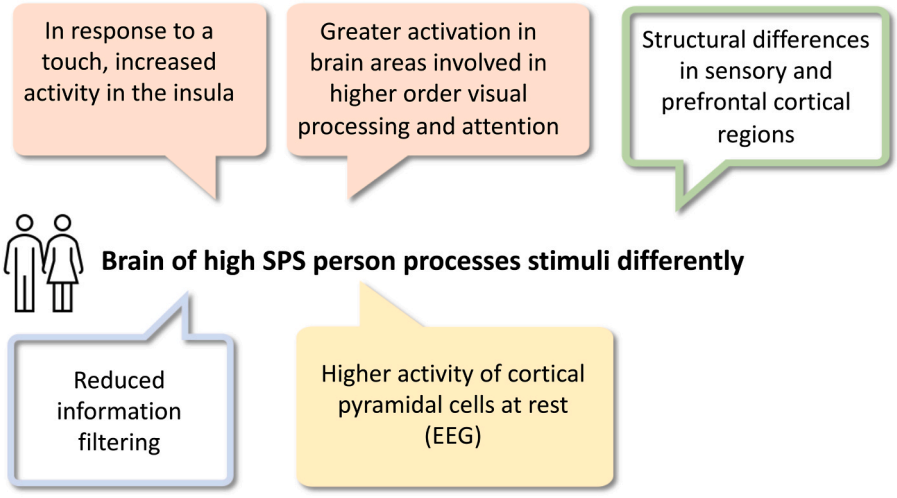

Fig. 3. Sensory-related neural characteristics of high SPS individuals.

sensitive persons processes sensory stimulation differently. An older study investigated how cultural differences influenced the judgment of visual stimuli in high versus low sensitive individuals. European–Americans and East-Asians underwent a visuo-spatial task that was either context dependent (depending on relative information, typically easier for East-Asians) or independent (depending on absolute information, typically easier for European Americans). Each group exhibited greater activation for the culturally non-preferred task in frontal and parietal regions. However, the individuals high in SPS showed culture independent brain activation (Aron et al., 2010). The data suggest that the high-SPS participants were processing both the relative and absolute conditions, by paying close attention to details of the stimulus. Potentially, the sensory information was less filtered by cultural background in the highly sensitive persons, allowing them to process the information more 'as it is'.

8.2. Serotonin transporter, dopamine D4 receptor and BDNF gene variance

The 5-HTTLPR s-allele and DRD4 7-repeat polymorphisms have been associated with functional and structural changes in areas implicated in emotion and reward processing, as extensively reviewed elsewhere (e.g. (Hariri et al., 2006; Homberg and Jagiellowicz, 2022; Padmanabhan and Luna, 2014)), while imaging results on sensory- or attention-related cortical areas are limited. Nonetheless, it was found that the number of 5-HTTLPR s-alleles was significantly correlated with functional connectivity of a visual-limbic subnetwork (Cao et al., 2018). Also, researchers reported that the 5-HTTLPR s-allele, compared to the 5-HTTLPR lallele, combined with cognitive effort was associated with an increase in a specific auditory event-related amplitude as measured by EEG, being indicative for increased attention (Enge et al., 2011). Likewise, a study focusing on preschoolers found that the 5-HTTLPR s-allele, compared to the l-allele, was associated with increased attention as measured by event-related potentials (Isbell et al., 2016). Using MR spectroscopy, lower levels of GABA were found in the thalamus of 5-HTTLPR s-allele versus l-allele carriers (Ellerbrock et al., 2021). In relation to the DRD4 7-repeat allele, lower late negative components in their EEG patterns were found, indicative for less distraction sensitivity due to less effective GABAergic inhibitory signaling (Birkas et al., 2006). In addition, this polymorphism has been associated with enhanced auditory evoked gamma responses, which the authors explained as reduced inhibitory signaling (Demiralp et al., 2007). Finally, the BDNF met-allele has been associated with increased performance of the tactual performance test, which was paralleled by changes in the functional connectivity between temporal, parietal and somatosensory cortices (Yang et al., 2017).

8.3. Summary

Human neuroimaging studies imply sensory-related cortical functional and structural brain differences as well as a reduction in inhibition in association with increased environmental sensitivity. While clearly more studies are needed to further clarify the level of plasticity in sensory-related brain regions, the current findings do carefully support the idea that increased environmental sensitivity is associated with reduced inhibitory signaling, being indicative for a young brain state at the level of sensory information processing.

9. Effects of experiences due to increased environmental sensitivity on sensitive periods

The development and maturation of sensory- and limbic areas is in the first place strongly driven by experiences, hence environmental factors. Therefore, it is well possible that increased environmental sensitivity per se, besides the factors that increase environmental sensitivity (section 1, 2), also influences the onset and duration of the experience-dependent sensitive periods. That is, a stronger 'perception' of environmental stimuli in highly sensitive individuals may affect the timing of sensitive periods. In other words, the environment stimuli and experiences that a highly sensitive individual is exposed to also influence sensitive periods, next to the genetic factors that shape increased environmental sensitivity. However, it is difficult to detangle if certain environmental factors increase environmental sensitivity through changes in sensitive periods in development, or that individuals respond differently to the environment because of their environmental sensitivity. Another item is that openness itself can lead to more curiosity driven behavior, and thereby exposure to more environmental stimulation, which in turn influences sensitive periods.

In light of the fact that the environment itself is also critical for sensitive periods in development, it is important to consider when interpretating animal data that the animals are living in shoebox-sized cages with minimal environmental enrichment in the laboratory, which strongly limits the sensory stimulation the animals are being exposed to and hinders the animals to display natural behaviors. The consequence is that conventional housing itself causes anxiety- and depression-like behavior (Cait et al., 2022). Hence, in the interpretation of the data derived from animal studies must take into account that the findings are only applicable to the laboratory environment. Indeed, it has been demonstrated that exposing laboratory rodents to a natural environment for 6 weeks alters the barrel cortex map of cages rats (Polley et al., 2004). Acute, multi-site extracellular recordings demonstrated suppressed evoked neuronal responses and smaller, sharper constituent receptive fields in the upper cortical layers (II/III), but not in the thalamic recipient layer (IV), of the barrel cortex in rats with naturalistic experience (Polley et al., 2004). It is well conceivable that changing the environment during the critical/sensitive period from the conventional lab cage to a (semi)-naturalistic one will be of influence on the timing of critical/sensitive periods and/or their plasticity, particularly in individuals showing increased environmental sensitivity.

10. Summary and conclusion

10.1. Summary and suggestions for future research

In summary, adult individuals displaying increased environmental sensitivity may bear a "younger" brain, due to delayed and potentially extended sensitive periods in the development of sensory-related brain regions (Fig. 1). Genes that increase environmental sensitivity seem to be associated with decreased cortical inhibition as well as increased excitability in adulthood, which is indicative for heightened plasticity as observed during sensitive periods. A systematic evaluation of critical/sensitive period plasticity markers across development, along with assessments of the responsivity to sensory stimulus deprivation and enrichment at different ages and causal manipulations is expected to further support the hypothesis. Given that the brain of humans is inaccessible, this requires animal research. Thus, future research requires the systematic assessment of sensitive period plasticity markers and responsivity to changes in sensory stimulation (e.g. whisker trimming or ocular dominance assessment after unilateral eye closure) at frequent intervals from P1 to P70 in the 5-HTT, DRD4 and BDNF knockout rodent models. In addition, causal manipulations such as GABA agonist treatment, chemogenetic-mediated up- or down-regulation of the activity of PV neurons, or conditional over expression of plasticity markers at critical timepoints in development, are needed to ascertain the link between plasticity markers and increased environmental sensitivity. Nonetheless the study of sensitive periods is also possible in humans. Such studies can include environmental manipulations, plasticity manipulations, and computational modeling together with EEG or neuroimaging measurements to examine neurophysiological correlates of these manipulations (Gabard-Durnam and McLaughlin, 2020). While manipulations like deprivation are ethically not allowed in humans, naturally occurring deprivation can be used to study sensitive periods.

For example, infants born deaf or with dense cataracts that occlude visual inputs have revealed sensitive periods in auditory, language, and visual development (Lewis and Maurer, 2005;Kral et al., 2019). Psychosocial deprivation associated with institutional rearing has also been used as a model for studying sensitive periods in humans (Nelson et al., 2019). A disadavatange of such deprivation studies in humans is that, particularly in case of psychological deprivation, there is no control over the precise nature of the sensory information that is being removed from the environment. Finally, given that antenatal SSRI treatment is common, to treat maternal depression, children whose mothers have been using SSRIs during pregnancy (Gingrich et al., 2017), could be followed-up for their sensitivity and responsivity to sensory stimulation at different ages.

The phenotypic changes in the animal models for increased environmental sensitivity, as described in Section 7, may provide further inspiration for measurements of sensitive periods in humans. Data suggest that serotonin-mediated plasticity changes may broaden the perceptual reach by including irrelevant information in the perceptual event, as was for instance indicated by a reduction in latent inhibition in 5-HTT knockout rats (Section 7). As a result, more information will flow into their sensory systems, and things will be observed that others block out. This possibility is supported by the finding that inhibition of GABA signaling in the prefrontal cortex inhibits latent inhibition (Piantadosi and Floresco, 2014). Furthermore individuals showing Openness to experience (Barford and Smillie, 2016; Antinori et al., 2017), and young children compared to older children (McLaren et al., 2021) show a reduction in latent inhibition. This may be comparable to the phenomenon that adults remember specifically the information they focus on and ignore the rest, while children pay attention to all the information they are presented, including irrelevant information (Plebanek and Sloutsky, 2017). Of further interest, in a binocular rivalry test, in which perception alternates between the two eyes and there is an ebb and flow of perception depending on the strength of inhibitory interactions between competitive neuronal populations in the visual cortex, it has been shown that individuals showing Openness to experience exhibit increased mixed percept in a binocular rivalry test (Antinori et al., 2017), that children experience more piecemeal rivalry (a type of mixed-percept) than adults (Hudak et al., 2011), and that increasing GABAergic inhibition increases perceptual suppression and reduces mixed-percept time (Mentch et al., 2019). Latent inhibition and binocular rivalry tests may thus may also aid in testing the hypothesis that increased environmental sensitivity is associated with delayed but extended sensitive periods in humans. In addition, tests assessing the threshold for detecting stimuli, such as the Taste Detection Threshold (Joseph et al., 2021) and the Quantitative sensory test (Mucke M and Radbruch, 2021), should be added to comprehensively understanding sensory processing alterations in individuals high in environmental sensitivity.

10.2. Conclusion

Through this review we hope that we have raised interest in furthering the knowledge of the brain mechanisms underlying increased environmental sensitivity. This will not only advance our fundamental understanding of brain plasticity and the emerge of individual differences in behavior and personalities, but will also contribute to more acceptance of the fact that we differ in the way we perceive the world around us to work towards a more inclusive society.

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Declaration of Competing interest

There is no conflict of interest

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None

Author contributions

JRH conceptualized and wrote the manuscript; FC wrote and edited the manuscript; GC and PB critically read and edited the manuscript.

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