

New perspectives on the neurodevelopmental effects of SSRIs

Judith R. Homberg^{1*}, Dirk Schubert^{1*} and Patricia Gaspar²

¹ Donders Institute for Brain, Cognition and Behaviour, Centre for Neuroscience, Department of Cognitive Neuroscience, Radboud University Nijmegen Medical Centre, Geert Grooteplein 21, 6525 EZ Nijmegen, The Netherlands

² INSERM, U839, Université Paris 6, Institut du fer à Moulin, 17 rue du fer à Moulin, Paris 5, France

Selective serotonin reuptake inhibitors (SSRIs) are widely prescribed for the treatment of depression and anxiety-related disorders. These drugs target the serotonin transporter (5-HTT) and increase serotonin signaling. Although chronic SSRI administration has few reported side effects, recent observations suggest that it could have long-term effects on neurodevelopment. First, 5-HTT is transiently expressed in many brain areas during development. Second, 5-HTT blockade during development causes wiring defects in these areas. These effects are seen most clearly in the sensory systems. Third, the behavioural effects of 5-HTT blockade during development are sometimes dramatically different from the effects of 5-HTT blockade during adulthood. Most of this evidence was collected from studies with 5-HTT knockout mice and rats. However, the phenotypes associated with low or high functioning 5-HTT alleles in humans can result from similar developmental alterations in 5-HT levels. Here, we review the existing evidence on the long-term effects of developmental SSRI exposure.

Introduction

Selective serotonin reuptake inhibitors (SSRIs) are among the most frequently prescribed drugs for the treatment of depression and anxiety-related disorders. These drugs inhibit the function of the serotonin transporter (5-HTT), which is responsible for the high affinity reuptake of serotonin (5-HT) at the plasma membrane. There is only one 5-HTT gene, and an identical protein is encoded in both the central nervous system and in peripheral tissues (e.g. gut or platelets). 5-HTT inhibition by SSRIs leads to an accumulation of 5-HT in the extracellular space. This increases the magnitude and duration of the activity of 5-HT on pre- and postsynaptic 5-HT receptors. There are 15 different 5-HT receptor subtypes, which can trigger a variety of signalling pathways. Current research indicates that a combination of several of these pathways is required for SSRI action. Furthermore, the long latency of onset for SSRI antidepressant action suggests that secondary effects, such as transcriptional changes and cellular plasticity mechanisms, are also necessary (for review see Ref. [1]).

The success of SSRIs relative to other antidepressants is as a result, in part, of their proven safety in adults. Therefore, SSRIs are the drug of choice for treating depressed

pregnant and postpartum women [2]. There is a 10–16% prevalence of depression during pregnancy [3]; 25% of depressed women continue antidepressant use, and another 0.5% start using antidepressants, during pregnancy [4]. As most SSRIs reach the foetus via the placenta [5] and are detectable in breast milk and breast-fed infants [6], a significant number of unborn and newborn children are exposed to SSRIs during critical phases of neurodevelopment.

Several longitudinal or retrospective studies in humans have investigated the potential hazards of SSRI exposure (see Ref. [7] for a recent review, Box 1), but these studies have largely focused on neonatal cardiovascular abnormalities [8], withdrawal syndrome [9], premature birth, low birthweight and pulmonary hypertension [8]. Therefore, our understanding of the long-term behavioural and

Glossary

Amygdala: the amygdalae are the almond-shaped groups of nuclei located deep within the medial temporal lobes of the brain in rodents and humans. They play a primary role in the processing and memory of emotional reactions and are considered to be part of the limbic system.

Barrel cortex: a specific organisation of neurons in the somatosensory cortex composed of thalamocortical axon terminals and layer IV neurons. One barrel in the cortex corresponds to one whisker on the snout. Whiskers are used in rodents for orientation and social contact [59]. The equivalent of the barrel cortex in humans is the primary somatosensory cortex, which mediates fine sensory discriminations (e.g. fingertip sensations).

5-HT: serotonin (5-HT) is a phylogenetically ancient signalling molecule that affects many important physiological and cognitive processes and is disrupted in almost all psychiatric disorders. Substantial evidence in mammals and invertebrates indicates that the serotonergic signalling pathway integrates both basic physiological functions, including circadian rhythms of food intake, sleep and reproductive activity, and elementary brain tasks, including sensory processing, cognition, emotion regulation and motor activity. The diversity of 5-HT functions results from the ability of 5-HT to act on 15 different receptors and to modulate the activity of other neurotransmitter systems.

5-HTTLPR: the human serotonin transporter-linked polymorphic region (5-HTTLPR) consists of long (l) and short (s) promoter regulatory variants. People with the s variant have reduced 5-HTT availability compared with people with the l variant. This polymorphism has been correlated with the personality trait neuroticism and various psychiatric conditions.

Medial prefrontal cortex: the medial prefrontal cortex (mPFC) is the anterior part of the brain in front of the motor and premotor cortex in both rodents and humans. This brain region has been implicated in planning complex cognitive behaviours, decision making and moderating correct social behaviour. The basic activity of the PFC is thought to be coordination of thoughts and actions with internal goals. Although the organisation of prefrontal subregions differs in rodents and primates, they are functionally comparable.

SSRIs: selective serotonin reuptake inhibitors (SSRIs), introduced in the mid-1980s, are currently the most frequently prescribed antidepressants. They block the transport of 5-HT and thereby increase the stimulation of 5-HT receptors.

SSRI paradox: SSRIs have anxiolytic and antidepressant effects in adults. However, there is evidence that early developmental exposure to SSRIs results in an increased risk of anxiety and depression.

Corresponding author: Homberg, J.R. (j.homberg@cns.umcn.nl)

* Both authors contributed equally..

Box 1. The hazards of developmental SSRI exposure in humans

SSRIs are widely used by depressed women, and because these antidepressants cross the placenta [54] the development of the unborn child could be affected. The literature indicates that maternal SSRI treatment during the first trimester leads to increased risk of cardiac abnormalities [8], and that third-trimester treatment leads to neonatal complications, such as neonatal withdrawal syndrome (irritability, rigidity, tremor and respiratory distress) [9], premature birth, low birthweight and pulmonary hypertension in the newborn child [8]. Although these observations suggest that SSRIs should be used with caution during pregnancy, a recent retrospective review [55] and meta-analysis [56] failed to find substantial increases in congenital heart disease (cardiac malformation, pulmonary hypertension, ventricular septal defects) among neonates prenatally exposed to SSRIs. These findings are reassuring, but few studies have addressed the long-term consequences of developmental SSRI exposure. It has been reported that there are no distinct effects of developmental SSRI exposure on cognitive functions in children up to the age of 6 years [57]. However, there are subtle alterations, such as blunted sensory responses [58] and impaired fine motor skills [11], in children prenatally exposed to SSRIs. It remains to be determined whether developmental SSRI exposure in humans leads to anxiety- and depression-related symptoms or personality traits that resemble those correlated with the human 5-HTT polymorphism (see section on the comparison between pharmacological and genetic 5-HTT downregulation).

cognitive outcomes of *in utero* and neonatal SSRI exposure in humans is limited. In contrast, there have been numerous reports demonstrating that perinatal administration of SSRIs causes anxiety- and depression-like behaviours (the ‘SSRI paradox’) in rodents, which persist into adulthood [10–13] (Table 1).

In this article, we begin by reviewing studies which have shown a broad expression of the cellular targets of SSRIs during brain development. We then review the behavioural effects of perinatal SSRI exposure in rodents and compare them to the effects of genetic 5-HTT downregulation. Finally, we suggest a link between these behavioural changes and various alterations in neural circuit wiring and function.

Cellular targets of SSRIs during development

Because the 5-HTT protein is the primary target of SSRIs, identifying the cell types that harbour this transporter during development is key to our understanding of the neurodevelopmental consequences of early SSRI exposure (Figure 1).

In the adult brain, 5-HTT expression is limited to the 5-HT producing neurons of the raphe nuclei. However, a much broader expression has been observed and exten-

Table 1. The paradoxical behavioural outcome of early versus adult chronic SSRI exposure in rodents

Symptom	Developmental SSRIs	Adult SSRIs	Refs
Anxiety/depression	Increased anxiety/depression	Decreased anxiety/depression	[10,13,29,34]
REM sleep	Increased REM sleep	Decreased REM sleep	[13,60]
Sensory	Blunted pain responses, reduced gap crossing	No effect	[32,61]
Learning	Improved spatial learning	No effect	[33,62]
	Increased cocaine-induced conditioned place preference	No data	[35]
Cardiovascular	Dilated cardiomyopathy	Cardiodepression and vasodilatation	[12,63]

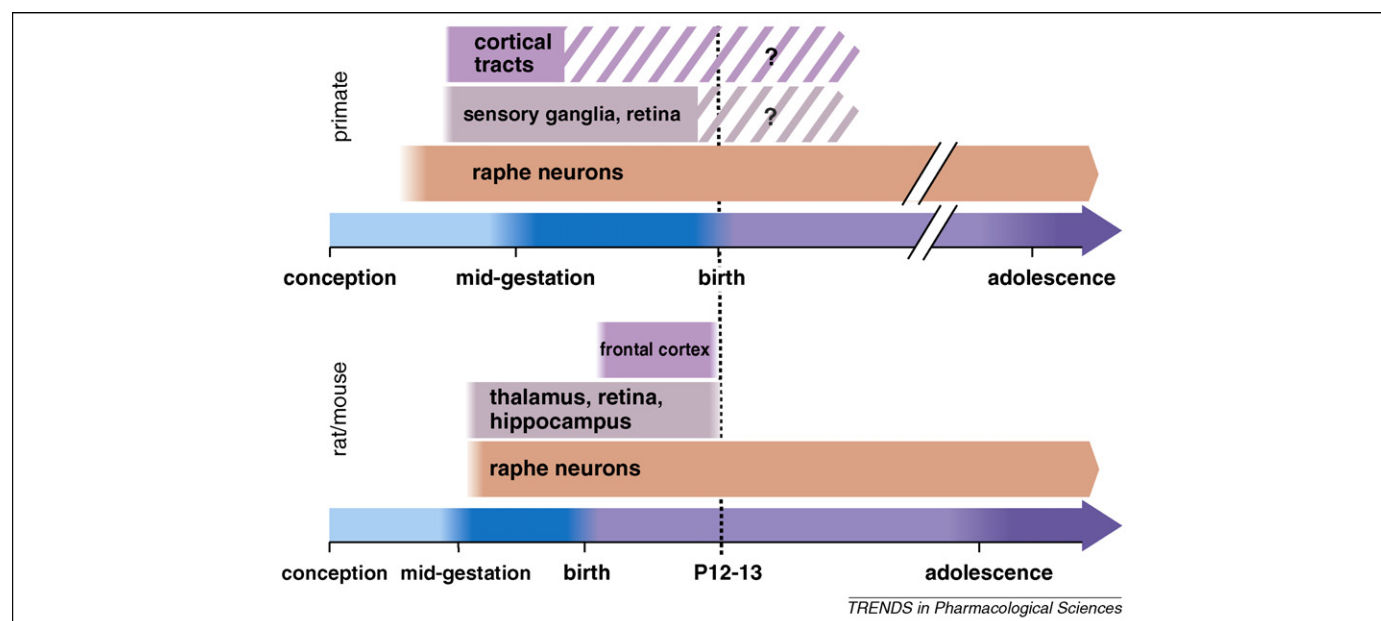


Figure 1. Time scale of 5-HTT expression in primates and rodents (mice and rats) during embryonic and early postnatal developmental periods. Note that in primates/humans the functional brain maturity at the day of birth is approximately postnatal day (P) 12–13 in rodents (indicated by dashed line) [64]. In human embryos (8–11 gestational weeks) 5-HTT is expressed in fibre tracts of the non-serotonergic internal capsule [17], and in marmosets (new world monkeys) 5-HTT appears in all major sensory afferents (dorsal root ganglia, retinal ganglion cells, cochlear nucleus and olfactory nerves) [18]. This transient expression of 5-HTT in non-serotonergic neurons corresponds to what has been described in greater detail in rodents. In mice and rats, 5-HTT expression appears at mid-gestation (E11) in the raphe nuclei, the origin of serotonergic neurons. 5-HTT is later expressed in non-serotonergic neurons in the sensory systems and limbic regions. This expression extends into the postnatal period. 5-HTT expression in the frontal cortex starts only after birth and ends rapidly during the second postnatal week, coinciding with the maturation of neural circuits [15]. It is the transient expression of 5-HTT in non-serotonergic neurons that might underlie the paradoxical behavioural outcome of early SSRI exposure.

Opinion

sively described in developing rodents (reviewed in Ref. [14]). Genetic fate mapping has recently permitted a more precise cellular localization of 5-HTT expression [15], making it possible to identify the principal targets of SSRIs during different phases of brain development. At mid-gestation (embryonic day 11, E11, in mice) expression of the 5-HTT gene begins in the 5-HT neurons of the raphe nuclei, but expression soon extends to non-serotonergic neurons, including the principal projection neurons of the sensory systems (thalamus, retina, somatosensory cortex), the corticolimbic pathways (hippocampus, E14–E15, and the prefrontal/cingulate cortex, postnatal day 0, P0). 5-HTT expression in non-serotonergic neurons ends rapidly during the second postnatal week, coinciding with the maturation of neural circuits. Repression of 5-HTT expression is controlled by circulating hormones, such as the thyroid hormone, which peak during postnatal life [16].

Although studies in humans are limited, they do provide further evidence for the broad developmental expression of 5-HTT. In 8–11 gestational week old embryos, 5-HTT is expressed in fibre tracts of the internal capsule and the optic tract. These fibres do not correspond to raphe projections [17]. In new world monkeys, 5-HTT was observed in all major sensory afferents (dorsal root ganglia, retinal ganglion cells, cochlear nucleus and olfactory nerves) at mid-gestation [18], a period which generally corresponds to the rodent perinatal period of neural circuit development. Unfortunately, the scarcity of biological material from primates has prevented evaluation of the precise time course of developmental 5-HTT expression, making it difficult to correlate these observations with the larger body of information collected from rodents.

Signalling pathways of 5-HT

5-HT exerts its neurotrophic actions through 5-HT receptors and their downstream signalling pathways. Almost all 5-HT receptors have been, in one way or another, implicated in the developmental functions of 5-HT, which include control of proliferation, migration, cell death and synaptogenesis (reviewed in Ref. [14]). The role of the 5-HTT could be particularly important in brain areas where it is colocalised with 5-HT receptors that signal various developmental processes. For instance, in thalamocortical cell axons the developmental expression pattern of the presynaptic 5-HT_{1B} receptor is similar to that of 5-HTT. These 5-HT_{1B} receptors regulate activity-dependent remodelling of the axons by controlling glutamate release and modulating cAMP production. Downstream protein kinase A-mediated signals are involved in the response of axons to appealing guidance factors, such as netrins [19], or to repellent molecules, such as ephrins [20]. Thus, blocking 5-HTT during development could disrupt these intricate mechanisms and result in an altered topographic map.

Blocking 5-HTT can also affect developmental processes via 5-HT_{1A} and 5-HT₂ receptors. In the medial prefrontal cortex (mPFC), 5-HTT is coexpressed with 5-HT_{2A} and 5-HT_{2C} receptors [21], which play a role in several late maturation events, such as developmental cell death [22] and dendritic maturation [23]. Furthermore, 5-HT_{1A} receptor antagonism during postnatal development blocked depression-like symptoms and reduced the rapid

eye movement (REM) sleep deficit normally observed in 5-HT transporter knockout (5-HTT^{-/-}) mice [24].

In summary, the transient developmental expression of 5-HTT in non-serotonergic neurons could explain some of the effects of early SSRI exposure. 5-HTT regulates 5-HT levels and thus determines the activation of pre- (5-HT_{1A/1B}) and postsynaptic (5-HT_{1A/2A/2C}) 5-HT receptors. Because the developmental 5-HTT expression disappears shortly after birth in all brain regions except for the raphe nuclei, the behavioural consequences of SSRI exposure depend on the developmental stage at which the exposure occurred, as highlighted in the following section.

Lessons from rodent behavioural studies

Initial studies showed that embryonic exposure to SSRIs in rats increased neonatal mortality [25] and reduced body weight [26]. 5-HTT [27] and 5-HT [28] expression and 5-HT_{2A/2C} receptor [26] density were reduced, indicating decreased 5-HT function. Hansen *et al.* [29] were the first to report that neonatal (P8–P21) exposure to the SSRI LU-10-134-C in rats resulted in depression-like symptoms during adulthood. Despite this alarming finding, it was the later work of Ansorge *et al.* [10] that triggered greater awareness of the potential detrimental effects of neonatal SSRI exposure. They showed that chronic SSRI treatment during postnatal days 4–21 resulted in reduced exploratory behaviour and increased anxiety-related phenotype, a phenotype which resembled that of 5-HTT^{-/-} mice. Neonatal SSRI exposure has also been shown to reduce aggression [30] and sexual behaviour [31], to increase REM sleep and anhedonia [13], and to blunt thermal and tactile responses [32]. Additional studies focusing on the effects of prenatal SSRI exposure revealed that offspring showed delayed motor development, improved spatial learning [33], reduced impulsivity, increased immobility in the forced swim test [34], increased sensitivity to the reinforcing effects of cocaine and reduced extinction of cocaine-seeking behaviour [35]. Together, these studies highlight two important points. First, it appears that both neonatal and prenatal SSRI exposure leads to anxiety- and depression-like symptoms during adulthood. Second, the effect of SSRI exposure on cognitive functions has not been extensively addressed.

In summary, the rodent studies indicate that SSRI exposure during an early developmental phase induces behavioural symptoms that oppose those induced by adult SSRI exposure (Table 1). These effects are hence termed “paradoxical”.

Genetic versus pharmacological 5-HTT downregulation in rodents

In addition to showing that neonatal SSRI exposure leads to paradoxical anxiety- and depression-related symptoms, Ansorge *et al.* [10] and Popa *et al.* [13] also demonstrated that these symptoms were strikingly similar to those of 5-HTT^{-/-} mice (and rats; for review see Ref. [36]). Indeed, developmental SSRI exposure causes a reduction in 5-HTT expression in adults [27] that imitates, in part, the genetic inactivation of 5-HTT. In addition to the anxiety- and depression-like symptoms, increased sensitivity to the reinforcing effects of cocaine, a failure to extinguish cocaine

self-administration, reduced aggression and blunted thermal responses have been reported in both 5-HTT^{-/-} [36–38] and perinatally exposed [30,32,35] rodents. However, there are some exceptions. For example, desensitization of the 5-HT_{1A} receptor is found in 5-HTT^{-/-} rodents [36] but not in mice treated with SSRIs as neonates [13].

The general similarities between 5-HTT knockout and prenatal/neonatal SSRI exposure imply that 5-HTT^{-/-} rodent findings can be used to ‘predict’ the outcome of early SSRI exposure. One prediction is that developmental exposure to SSRIs can result in improved decision making and cognitive flexibility. 5-HTT^{-/-} rodents show reduced long-term object recognition memory, increased recall of fear memory and increased decision making under ambiguity [36]. Thus, the outcome of early SSRI treatment can also have positive components. Consistent with these results, Bairy *et al.* [33] reported improved spatial learning in rats exposed to fluoxetine prenatally.

In summary, the effects of developmental SSRI exposure are, to a large extent, mimicked by genetic 5-HTT downregulation, implying that 5-HTT^{-/-} rodents can be used as a model to help predict the behavioural effects of SSRI exposure during development. This also applies to our understanding of the neuroanatomical consequences of developmental SSRI exposure.

The neuroanatomical correlates of the paradoxical behavioural outcomes in rodents

Insight into the underlying anatomical and physiological correlates of the behavioural changes caused by early SSRI administration is still limited. However, using evidence

from studies with 5-HTT^{-/-} rodents, it is possible to link the paradoxical behavioural outcomes of developmental SSRI exposure to two main neural networks: the somatosensory cortex and the corticolimbic circuit.

Somatosensory cortex

Possibly the clearest case is the rodent somatosensory cortex, where a link between developmental SSRI exposure, anatomical changes and sensory functions is emerging (Figure 2). The primary somatosensory cortex comprises anatomical modules in layer IV, called ‘barrels’, which correspond to functional inputs from whiskers on the contralateral snout in a one-to-one relationship [39]. The barrel centres are projection targets of thalamocortical axons (TCAs) that conduct sensory information and form terminal clusters in layer IV. Neurons in layer IV that receive synaptic contacts from TCAs organise around the terminal clusters and form the ‘barrel walls’. 5-HTT^{-/-} mice have structural and functional abnormalities in the barrels, and the density of somatosensory cortical neurons is altered in these animals [40–43].

Somewhat comparable abnormalities result from SSRI treatment in developing (P0–P6) rats [32]. Treated rats showed thinned out terminal clusters of TCAs in layer IV barrels and altered dendritic organization of the spiny stellate neurons, the dominant population of excitatory neurons in the barrels. Furthermore, sensorimotor learning deficits in the gap crossing test suggest that the treated rats have impaired transmission of tactile information to the primary somatosensory cortex [32]. However, rats do not completely lose their tactile skills. With a distorted

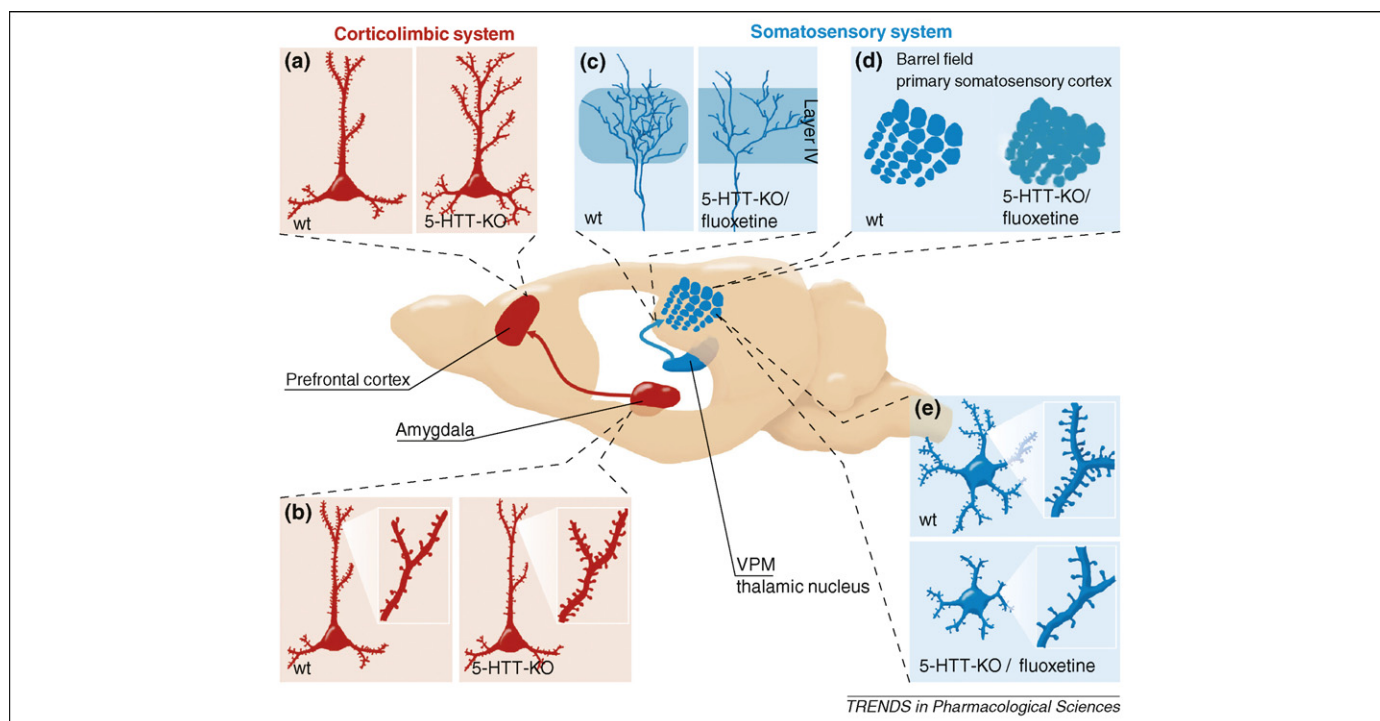


Figure 2. Known structural effects of impaired 5-HT transporter activity in the rodent brain. 5-HT transporter (5-HTT) dysfunction during early brain development results in distinct changes in corticolimbic (red) and somatosensory thalamocortical (blue) structures. In the corticolimbic system, knockout of 5-HTT leads (a) to increased dendritic spine densities in pyramidal cells of the amygdala and (b) abnormally increased dendritic branching in pyramidal neurons of the prefrontal cortex [50]. In the somatosensory systems, knockout of 5-HTT as well as exposure to SSRIs (fluoxetine) during early development causes (c) impaired innervation of cortical layer IV by distinctively reduced arborisation of thalamocortical axon clusters, (d) diffuse barrel patterns and (e) dendritically smaller spiny stellate cells with a reduced spine density [34,45–47]. Brain regions and related pathways, which are noted for rodents here, have analogues in human brains with comparable or identical nomenclature and function. The rodent barrel cortex is, to some extent, structurally comparable to the representation of finger digits in the human primary somatosensory cortex.

Opinion

structural organization of thalamocortical innervations, it currently remains unclear how the intracortical networks can still extract and interpret incoming tactile information. One possible explanation is that neurons, e.g. in layer IV, can partially adapt to the disturbed tactile information transmission by structurally reorganizing their cell type-specific intracortical connectivity [44].

Corticolimbic circuit

A key corticolimbic circuit modulated by the serotonergic system is the circuit that connects the dorsal raphe nucleus, the mPFC and the amygdala. This circuit is of great interest as it is involved in stress-related responses in rodents and stress-related diseases in humans [36,45–47]. In 5-HTT^{-/-} rodents, alterations in the morphology of pyramidal neurons in the prefrontal cortex and amygdala were reported, which probably have a developmental origin (Figure 2). These structural changes are correlated to decreased recall of fear extinction [48]. Furthermore, programmed cell death is reduced in 5-HTT^{-/-} mice in several corticolimbic structures [49]. These changes are believed to reflect neurodevelopmental adaptations, but studies showing that developmental SSRI exposure leads to comparable changes are still needed to support this hypothesis.

Alterations of these two major neural networks can underlie the blunted somatosensation and increased anxiety- and depression-like symptoms in prenatally/neonatally SSRI exposed rodents. However, subtle alterations of other unexplored pathways could also participate in the behavioural alterations observed following developmental SSRI exposure. Further research is required in preclinical models to provide evidence for direct links between brain and behaviour before we can draw conclusions about the effects of developmental SSRI exposure in humans.

Concluding remarks

Current knowledge of the potential adverse consequences of SSRI use during pregnancy or the postpartum period, as summarised here, is still too limited to either conclude that SSRI use for pregnant women is safe or to recommend discontinuation of SSRI use during pregnancy. However, analysis of the current literature indicates several interesting directions that require further investigation.

First, a direct link between the neuroanatomical and behavioural correlates of developmental SSRI exposure in rodents still needs to be established.

Second, more research is required to draw conclusions about human SSRI use from rodent studies. For example, a more detailed expression map of 5-HTT gene expression during human development will be necessary for the determination of critical developmental phases during which SSRI exposure could be harmful. At this time, the effects of early SSRI exposure in humans can, to some extent, be predicted from studies of humans carrying the short (s) allelic variant of the 5-HTT promoter (5-HTTLPR). The s allele is associated with reduced expression of 5-HTT in blood cells [50] and increased stress responsivity in newborns [51]. Adult carriers of the s allele show increased amygdala reactivity [52] and changes in the functional coupling between the prefrontal cortex and amygdala [47], which are correlated with increased emotional reac-

tivity. Because the effects of 5-HTTLPR on behaviour are relatively modest and modulate personality traits within a normal range, the outcome of SSRI exposure might not be as adverse as animal studies suggest. However, results from animal studies and knowledge of 5-HTT expression in developing primates indicate that further investigation of 5-HTTLPR modulation of sensory systems is needed.

Third, concerns about the potential adverse effects of prenatal or neonatal SSRI exposure should be balanced by observations that untreated depression could also harm the unborn or newborn child. A current limitation of the animal models is that SSRIs are applied to healthy pregnant dams, which do not fully represent the human situation. Moreover, it is well established that the 5-HTTLPR-s allele modulates the antidepressant effects of SSRIs [53]. Thus, it is possible that the 5-HTTLPR genotype of the mother and child could also affect the outcome of early SSRI exposure.

As upcoming research improves our understanding of the role of 5-HT in neurodevelopment, more information about the long-term consequences of SSRI use during pregnancy and the postpartum period will allow doctors and patients to make better informed decisions.

Acknowledgements

We thank Sara Trowbridge for her useful comments on the manuscript. The work of J.H. is supported by The Netherlands Organisation for Scientific Research (NWO), grant # 91676160. P.G. is funded by the INSERM, University Paris 6, the Agence Nationale de la Recherche (ANR605-neur-046) and the European Commission (FP7-health-2007-A-201714).

References

- Krishnan, V. *et al.* (2008) The molecular neurobiology of depression. *Nature* 455, 894–902
- Nonacs, R. *et al.* (2003) Assessment and treatment of depression during pregnancy: an update. *Psychiatr. Clin. North Am.* 26, 547–562
- Bennett, H.A. *et al.* (2004) Prevalence of depression during pregnancy: systematic review. *Obstet. Gynecol.* 103, 698–709
- Ververs, T. *et al.* (2006) Prevalence and patterns of antidepressant drug use during pregnancy. *Eur. J. Clin. Pharmacol.* 62, 863–870
- Rampono, J. *et al.* (2004) A pilot study of newer antidepressant concentrations in cord and maternal serum and possible effects in the neonate. *Int. J. Neuropsychopharmacol.* 7, 329–334
- Kristensen, J.H. *et al.* (1999) Distribution and excretion of fluoxetine and norfluoxetine in human milk. *Br. J. Clin. Pharmacol.* 48, 521–527
- Alwan, S. *et al.* (2009) Safety of selective serotonin reuptake inhibitors in pregnancy. *CNS Drugs* 23, 493–509
- Chambers, C.D. *et al.* (2006) Selective serotonin-reuptake inhibitors and risk of persistent pulmonary hypertension of the newborn. *N. Engl. J. Med.* 354, 579–587
- Koren, G. *et al.* (2009) Adverse effects in neonates exposed to SSRIs and SNRI in late gestation – Motherisk Update 2008. *Can. J. Clin. Pharmacol.* 16, e66–e67
- Ansorge, M.S. *et al.* (2004) Early-life blockade of the 5-HT transporter alters emotional behavior in adult mice. *Science* 306, 879–881
- Casper, R.C. *et al.* (2003) Follow-up of children of depressed mothers exposed or not exposed to antidepressant drugs during pregnancy. *J. Pediatr.* 142, 402–408
- Noorlander, C.W. *et al.* (2008) Modulation of serotonin transporter function during fetal development causes dilated heart cardiomyopathy and lifelong behavioral abnormalities. *PLoS One* 3, e2782
- Popa, D. *et al.* (2008) Lasting syndrome of depression produced by reduction in serotonin uptake during postnatal development: evidence from sleep, stress, and behavior. *J. Neurosci.* 28, 3546–3554
- Gaspar, P. *et al.* (2003) The developmental role of serotonin: news from mouse molecular genetics. *Nat. Rev. Neurosci.* 4, 1002–1012
- Narbox-Nême, N. *et al.* (2008) Serotonin transporter transgenic (SERT^{Ter}) mouse line reveals developmental targets of serotonin specific reuptake inhibitors (SSRIs). *Neuropharmacology* 55, 994–1005

- 16 Berbel, P. *et al.* (2001) Role of thyroid hormones in the maturation and organisation of rat barrel cortex. *Neuroscience* 107, 383–394
- 17 Verney, C. *et al.* (2002) Changing distribution of monoaminergic markers in the developing human cerebral cortex with special emphasis on the serotonin transporter. *Anat. Rec.* 267, 87–93
- 18 Lebrand, C. *et al.* (2006) Transitory uptake of serotonin in the developing sensory pathways of the common marmoset. *J. Comp. Neurol.* 499, 677–689
- 19 Bonnin, A. *et al.* (2007) Serotonin modulates the response of embryonic thalamocortical axons to netrin-1. *Nat. Neurosci.* 10, 588–597
- 20 Nicol, X. *et al.* (2006) Requirement of adenylate cyclase 1 for the ephrin-A5-dependent retraction of exuberant retinal axons. *J. Neurosci.* 26, 862–872
- 21 Cornea-Hebert, V. *et al.* (1999) Cellular and subcellular distribution of the serotonin 5-HT_{2A} receptor in the central nervous system of adult rat. *J. Comp. Neurol.* 409, 187–209
- 22 Stankovski, L. *et al.* (2007) Developmental cell death is enhanced in the cerebral cortex of mice lacking the brain vesicular monoamine transporter. *J. Neurosci.* 27, 1315–1324
- 23 Vitalis, T. *et al.* (2007) Embryonic depletion of serotonin affects cortical development. *Eur. J. Neurosci.* 26, 331–344
- 24 Alexandre, C. *et al.* (2006) Early life blockade of 5-hydroxytryptamine 1A receptors normalizes sleep and depression-like behavior in adult knock-out mice lacking the serotonin transporter. *J. Neurosci.* 26, 5554–5564
- 25 Vorhees, C.V. *et al.* (1994) A developmental neurotoxicity evaluation of the effects of prenatal exposure to fluoxetine in rats. *Fundam. Appl. Toxicol.* 23, 194–205
- 26 Cabrera, T.M. *et al.* (1994) Delayed decreases in brain 5-hydroxytryptamine_{2A/2C} receptor density and function in male rat progeny following prenatal fluoxetine. *J. Pharmacol. Exp. Ther.* 269, 637–645
- 27 Hansen, H.H. *et al.* (1998) Long-term effects on serotonin transporter mRNA expression of chronic neonatal exposure to a serotonin reuptake inhibitor. *Eur. J. Pharmacol.* 352, 307–315
- 28 Cabrera-Vera, T.M. *et al.* (1997) Effect of prenatal fluoxetine (Prozac) exposure on brain serotonin neurons in prepubescent and adult male rat offspring. *J. Pharmacol. Exp. Ther.* 280, 138–145
- 29 Hansen, H.H. *et al.* (1997) Neonatal administration of the selective serotonin reuptake inhibitor Lu 10-134-C increases forced swimming-induced immobility in adult rats: a putative animal model of depression? *J. Pharmacol. Exp. Ther.* 283, 1333–1341
- 30 Manhães de Castro, R. *et al.* (2001) Reduction of intraspecific aggression in adult rats by neonatal treatment with a selective serotonin reuptake inhibitor. *Braz. J. Med. Biol. Res.* 34, 121–124
- 31 Maciag, D. *et al.* (2006) Neonatal antidepressant exposure has lasting effects on behavior and serotonin circuitry. *Neuropsychopharmacology* 31, 47–57
- 32 Lee, L.J. (2009) Neonatal fluoxetine exposure affects the neuronal structure in the somatosensory cortex and somatosensory-related behaviors in adolescent rats. *Neurotox. Res.* 15, 212–223
- 33 Bairy, K.L. *et al.* (2007) Developmental and behavioral consequences of prenatal fluoxetine. *Pharmacology* 79, 1–11
- 34 Lisboa, S.F. *et al.* (2007) Behavioral evaluation of male and female mice pups exposed to fluoxetine during pregnancy and lactation. *Pharmacology* 80, 49–56
- 35 Forcelli, P.A. *et al.* (2008) Teratogenic effects of maternal antidepressant exposure on neural substrates of drug-seeking behavior in offspring. *Addict. Biol.* 13, 52–62
- 36 Kalueff, A.V. *et al.* Conserved role for the serotonin transporter gene in rat and mouse neurobehavioral endophenotypes. *Neurosci. Biobehav. Rev.* [epub ahead of print, doi:10.1016/j.neubiorev.2009.08.003]
- 37 Homberg, J.R. *et al.* (2008) Adaptations in pre- and postsynaptic 5-HT_{1A} receptor function and cocaine supersensitivity in serotonin transporter knockout rats. *Psychopharmacology (Berl.)* 200, 367–380
- 38 Vogel, C. *et al.* (2003) Absence of thermal hyperalgesia in serotonin transporter-deficient mice. *J. Neurosci.* 23, 708–715
- 39 Woolsey, T.A. *et al.* (1970) The structural organization of layer IV in the somatosensory region (SI) of mouse cerebral cortex. The description of a cortical field composed of discrete cytoarchitectonic units. *Brain Res.* 17, 205–242
- 40 Persico, A.M. *et al.* (2001) Barrel pattern formation requires serotonin uptake by thalamocortical afferents, and not vesicular monoamine release. *J. Neurosci.* 21, 6862–6873
- 41 Salichon, N. *et al.* (2001) Excessive activation of serotonin (5-HT) 1B receptors disrupts the formation of sensory maps in monoamine oxidase a and 5-HT transporter knock-out mice. *J. Neurosci.* 21, 884–896
- 42 Altamura, C. *et al.* (2007) Altered neocortical cell density and layer thickness in serotonin transporter knockout mice: a quantitation study. *Cereb. Cortex* 17, 1394–1401
- 43 Esaki, T. *et al.* (2005) Developmental disruption of serotonin transporter function impairs cerebral responses to whisker stimulation in mice. *Proc. Natl. Acad. Sci. U. S. A.* 102, 5582–5587
- 44 Schubert, D. *et al.* (2007) Mapping functional connectivity in barrel-related columns reveals layer- and cell type-specific microcircuits. *Brain Struct. Funct.* 212, 107–119
- 45 Hariri, A.R. *et al.* (2006) Genetics of emotional regulation: the role of the serotonin transporter in neural function. *Trends Cogn. Sci.* 10, 182–191
- 46 Heinz, A. *et al.* (2005) Amygdala-prefrontal coupling depends on a genetic variation of the serotonin transporter. *Nat. Neurosci.* 8, 20–21
- 47 Pezawas, L. *et al.* (2005) 5-HTTLPR polymorphism impacts human cingulate-amygdala interactions: a genetic susceptibility mechanism for depression. *Nat. Neurosci.* 8, 828–834
- 48 Wellman, C.L. *et al.* (2007) Impaired stress-coping and fear extinction and abnormal corticolimbic morphology in serotonin transporter knockout mice. *J. Neurosci.* 27, 684–691
- 49 Persico, A.M. *et al.* (2003) Reduced programmed cell death in brains of serotonin transporter knockout mice. *Neuroreport* 14, 341–344
- 50 Lesch, K.P. *et al.* (1996) Association of anxiety-related traits with a polymorphism in the serotonin transporter gene regulatory region. *Science* 274, 1527–1531
- 51 Mueller, A. *et al.* (2009) The role of the serotonin transporter polymorphism for the endocrine stress response in newborns. *Psychoneuroendocrinology*. [epub ahead of print, doi:10.1016/j.psyneuen.2009.07.002]
- 52 Canli, T. *et al.* (2007) Long story short: the serotonin transporter in emotion regulation and social cognition. *Nat. Neurosci.* 10, 1103–1109
- 53 Serretti, A. *et al.* (2007) Meta-analysis of serotonin transporter gene promoter polymorphism (5-HTTLPR) association with selective serotonin reuptake inhibitor efficacy in depressed patients. *Mol. Psychiatry* 12, 247–257
- 54 Rampono, J. *et al.* (2009) Placental transfer of SSRI and SNRI antidepressants and effects on the neonate. *Pharmacopsychiatry* 42, 95–100
- 55 Wichman, C.L. *et al.* (2009) Congenital heart disease associated with selective serotonin reuptake inhibitor use during pregnancy. *Mayo Clin. Proc.* 84, 23–27
- 56 Einarsson, A. *et al.* (2008) Evaluation of the risk of congenital cardiovascular defects associated with use of paroxetine during pregnancy. *Am. J. Psychiatry* 165, 749–752
- 57 Nulman, I. *et al.* (2002) Child development following exposure to tricyclic antidepressants or fluoxetine throughout fetal life: a prospective, controlled study. *Am. J. Psychiatry* 159, 1889–1895
- 58 Oberlander, T.F. *et al.* (2005) Pain reactivity in 2-month-old infants after prenatal and postnatal serotonin reuptake inhibitor medication exposure. *Pediatrics* 115, 411–425
- 59 Glassman, R.B. (1994) Behavioral specializations of SI and SII cortex: a comparative examination of the neural logic of touch in rats, cats, and other mammals. *Exp. Neurol.* 125, 134–141
- 60 Ivarsson, M. *et al.* (2005) Antidepressants and REM sleep in Wistar-Kyoto and Sprague-Dawley rats. *Eur. J. Pharmacol.* 522, 63–71
- 61 Mochizuki, D. (2004) Serotonin and noradrenaline reuptake inhibitors in animal models of pain. *Hum. Psychopharmacol.* 19 (Suppl. 1), S15–S19
- 62 Valluzzi, J.A. *et al.* (2007) Effects of fluoxetine on hippocampal-dependent and hippocampal-independent learning tasks. *Behav. Pharmacol.* 18, 507–513
- 63 Pacher, P. *et al.* (1998) Review of cardiovascular effects of fluoxetine, a selective serotonin reuptake inhibitor, compared to tricyclic antidepressants. *Curr. Med. Chem.* 5, 381–390
- 64 Romijn, H.J. *et al.* (1991) At what age is the developing cerebral cortex of the rat comparable to that of the full-term newborn human baby? *Early Hum. Dev.* 26, 61–67