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REVIEW

Monoamine-Sensitive Developmental Periods Impacting Adult Emotional and Cognitive Behaviors

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Development passes through sensitive periods, during which plasticity allows for genetic and environmental factors to exert indelible influence on the maturation of the organism. In the context of central nervous system development, such sensitive periods shape the formation of neurocircuits that mediate, regulate, and control behavior. This general mechanism allows for development to be guided by both the genetic blueprint as well as the environmental context. While allowing for adaptation, such sensitive periods are also vulnerability windows during which external and internal factors can confer risk to disorders by derailing otherwise resilient developmental programs. Here we review developmental periods that are sensitive to monoamine signaling and impact adult behaviors of relevance to psychiatry. Specifically, we review (1) a serotonin-sensitive period that impacts sensory system development, (2) a serotonin-sensitive period that impacts cognition, anxiety- and depression-related behaviors, and (3) a dopamine- and serotonin-sensitive period affecting aggression, impulsivity and behavioral response to psychostimulants. We discuss preclinical data to provide mechanistic insight, as well as epidemiological and clinical data to point out translational relevance. The field of translational developmental neuroscience has progressed exponentially providing solid conceptual advances and unprecedented mechanistic insight. With such knowledge at hand and important methodological innovation ongoing, the field is poised for breakthroughs elucidating the developmental origins of neuropsychiatric disorders, and thus understanding pathophysiology. Such knowledge of sensitive periods that determine the developmental trajectory of complex behaviors is a necessary step towards improving prevention and treatment approaches for neuropsychiatric disorders.

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INTRODUCTION

Neuronal activity during development shapes functional connectivity between neurons and thus determines the 'wiring' of the mammalian brain. As best described for the development of sensory systems, such plasticity is often restricted to specific developmental periods, so-called sensitive periods. If certain events must occur within specified time windows to allow for normal maturation, respective time windows are referred to as critical periods. The best-studied example is the critical period for the formation of ocular dominance columns, when retinal activity determines columnar size (Espinosa and Stryker, 2012; Hensch, 2005). Sensitive or critical period plasticity allows for circuit maturation to respond/adapt to external (environmental) and internal (genetic) factors. Although adaptive from an evolutionary perspective, heightened plasticity during sensitive periods also permits environmental and genetic factors to shift ontogenetic pathways and confer risk for disorders.

Here we review developmental periods that are sensitive to monoamine signaling and influence adult behavior of important relevance for psychiatry. First, we provide a short overview of dopamine (DA) and serotonin (5-HT) system development, because this information relates to mechanistic aspects of monoamine-sensitive periods. We then briefly review the murine neonatal 5-HT-sensitive period with consequences on sensory system development, because these findings provide the best-characterized examples of stark neuroanatomical malleability and reveal guiding conceptual principles that relate to monoamine-sensitive periods in general. Thereafter, we focus on two periods: the murine early postnatal period, highlighting its role in shaping adult anxiety/depression-related behaviors and cognition, and the murine periadolescent (PA) period, highlighting monoamine signaling-related consequences on adult aggression and behavioral stimulant sensitivity. For both periods, we review preclinical data to provide mechanistic insight, as well as epidemiological and clinical data to point out translational relevance. The murine embryonic period is reviewed by Stanwood *et al* in this issue.

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MONOAMINE SYSTEM DEVELOPMENT

In humans, 5-HT neurons are first detected when the embryo is 5 weeks old (Sundstrom *et al*, 1993), with rapid growth and proliferation until the 10th week of gestation (Levallois *et al*, 1997). After 15 weeks of gestation, 5-HT cell bodies cluster in the raphe nuclei (Takahashi *et al*, 1986). Levels of 5-HT increase during the first 2 years and then decline to adult levels after the age of 5 years (Sodhi and Sanders-Bush, 2004). In rodents, this dynamic maturation of the 5-HT system is also present (Figure 1). The first 5-HT neurons appear at the 12th day of rodent gestation (Lauder and Bloom, 1974). 5-HTergic neurons start releasing 5-HT on embryonic day 13 (E13) (Lambe *et al*, 2000; Lidov and Molliver, 1982a), and levels of 5-HT peak within the first postnatal week, after which they decline, reaching adult levels at around postnatal day 15 (P15; Hohmann *et al*, 1988). 5-HTergic neurons continue to elaborate their innervation patterns throughout the embryonic and early postnatal life, until about P21 (Lauder, 1990). Hence, in mice and rats, the presynaptic 5-HT components surface around E12 and mature until about P21. An additional aspect of presynaptic 5-HTergic system maturation is the transient adoption of a 5-HTergic phenotype by several otherwise non-5-HTergic neuron populations during late embryonic and early postnatal development (Gaspar *et al*, 2003; Lebrand *et al*, 1996, 1998; Salichon *et al*, 2001). Lastly, 5-HT receptors are expressed early in embryonic development, even before 5-HTergic afferents reach their innervation targets (Bonnin *et al*, 2006; Hellendall *et al*, 1993). During these early developmental stages, 5-HT arising from placental sources acts on 5-HT heteroreceptors, enabling developmental 5-HT signaling even before 5-HTergic axons have reached their targets (Bonnin *et al*, 2011).

Midbrain DA neurons appear during the second month of gestation in humans, and between E12 and E15 in rodents (Olson and Seiger, 1972). In rats, starting at E15, DA-positive fibers pass through the developing striatum to cortical regions. The development of cortical DA innervation continues to increase until P60, after which density and topography of DAergic afferents remain constant (Kalsbeek *et al*, 1988). Interestingly, several measures of DAergic system maturation transiently peak during adolescence (Figure 1). For example, DA transporter (DAT) density in the striatum increases from P25 through P50, but then decreases continuously until P90 (Moll *et al*, 2000; Tarazi *et al*, 1998a). DA receptors are first expressed by E14 in the rat and E12 in the mouse (Araki *et al*, 2007; Jung and Bennett, 1996), and during postnatal development, striatal DA receptor-binding capacity continues to gradually increase until P28–P40, after which it diminishes again to reach stable levels at around P60 (Giorgi *et al*, 1987; Tarazi *et al*, 1998b; Teicher *et al*, 1995). Likewise, DAergic cell activity in mice is low at weaning, then increases to a peak at P45, after which it declines once again (McCutcheon and Marinelli, 2009). In the ventral tegmental area (VTA), this transient increase in DAergic activity is characterized by increased non-bursting activity and longer burst duration (McCutcheon *et al*, 2012). Lastly, tissue DA levels peak between P25 and P40 (Noisin and Thomas, 1988). Hence, pre- and postsynaptic DA system maturation follows an expansion–contraction course, peaking during late adolescence.

Due to the expression of the pre- and postsynaptic components of the 5-HT and DA systems during development, with monoaminergic neurons innervating and releasing neurotransmitter, and with extraneuronal sources providing central monoamines, it is easily conceivable that 5-HT and DA have a critical role in modulating neurodevelopment and functional circuit formation. Animal studies support this hypothesis, and have uncovered consequences of dysregulated developmental monoamine signaling on

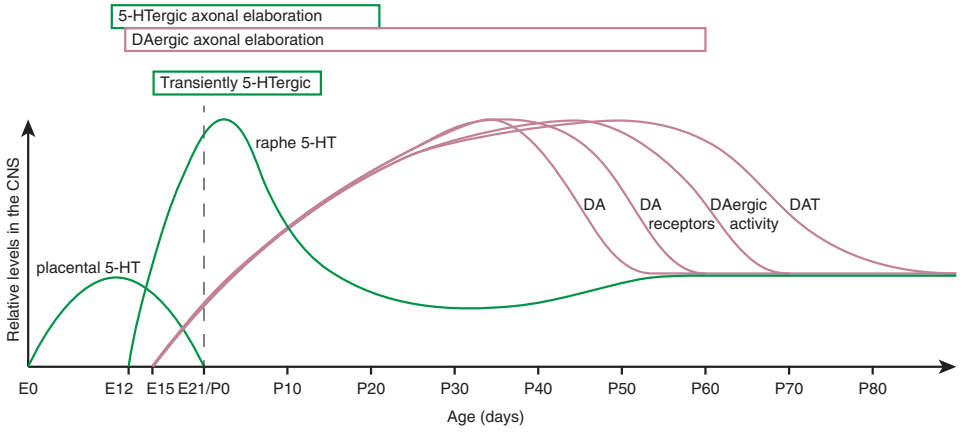


Figure 1. Transient peaks in monoamine system development. The graph displays relative levels of 5-HTergic and DAergic measures in the CNS across rat and mouse development: monoamine tissue concentration (5-HT of placental and raphe origin and DA), DA receptor binding (DA receptors) DAergic firing frequency (DAergic activity), and DAT binging (DAT). Green labels 5-HTergic aspects, and red labels DAergic aspects. The dashed line separates embryonic (left) from postnatal (right) development. 'Transiently 5-HTergic' demarks the time window during which non-5-HTergic neurons transiently adopt a 5-HTergic phenotype. CNS, cerebrospinal fluid; DA, dopamine; 5-HT, serotonin.

cytoarchitecture and -physiology, neuronal circuit properties, and behavior. Interestingly and counter intuitively, too much monoamine signaling seems to be more disruptive to normal development than too little.

A 5-HT-SENSITIVE DEVELOPMENTAL PERIOD IMPACTING THE SOMATOSENSORY AND VISUAL SYSTEM

During embryonic and postnatal development, monoamines modulate neurodevelopmental processes such as cell division, migration and differentiation, axonal and dendritic elaboration and connectivity, and myelination and apoptosis (Gaspar *et al*, 2003; Haydon *et al*, 1984, 1987; Lauder, 1990; McCarthy *et al*, 2007; Popolo *et al*, 2004; Tarazi *et al*, 1998b; Teicher *et al*, 1995). 5-HT, eg, exerts prominent autoregulatory control in dorsal and median raphe nuclei formation during embryonic development by acting on 5-HT_{1A} and 5-HT_{1B} autoreceptors to limit the number of 5-HTergic neurons (Rumajogee *et al*, 2004). An example for heteroregulation of fundamental developmental processes is its modulatory effect on axonal guidance factors. Through 5-$HT_{1B/1D}$ heteroreceptors, 5-HT reverses the attraction exerted by netrin-1 on the developing posterior dorsal thalamic axons into repulsion, thereby contributing to patterning of thalamocortical connections in the developing brain (Bonnin *et al*, 2007). The two most prominent examples for 5-HTergic modulation of cortical and subcortical brain organization on a system-wide level relate to somatosensory and visual system formation.

5-HT and Somatosensory System Development

The rodent somatosensory cortex (SSC) contains barrel fields, with individual barrels representing single processing units for each vibrissa (reviewed in (Erzurumlu and Gaspar, 2012; Inan and Crair, 2007; Petersen, 2007; van Kleef *et al*, 2012)). Barrels reside in layer IV and are organized around thalamocortical projections from the ventroposteromedial (VPM) nucleus of the thalamus (Killackey, 1973). Thalamocortical VPM neurons transiently express *5-HTT* and vesicular monoamine transporter 2 (*VMAT2*) from E15 to P10, allowing for 5-HT uptake and vesicular storage (Hansson *et al*, 1998; Lebrand *et al*, 1996; Lebrand *et al*, 1998). The transient expression of *5-HTT* and the maintenance of low local 5-HT levels is critical for the formation of the barrel fields, as monoamine oxidase A (*MAOA*) or *5-HTT*-knockout mice fail to develop barrel fields (Cases *et al*, 1996; Persico *et al*, 2001). The sensitive period for 5-HTergic modulation of barrel field formation has been mapped to P0–P4 (Vitalis *et al*, 1998).

The proposed mechanism by which excess 5-HT leads to disruption of barrel field formation involves 5-HT_{1B} receptors, also transiently expressed by thalamocortical afferents during the first postnatal week in rodents (Bennett-Clarke *et al*, 1993). VPM 5-HT_{1B} receptors are located on axon terminals and inhibit the release of glutamate relative to incoming stimuli (Laurent *et al*, 2002; Mooney *et al*, 1994). Yet, such glutamatergic synaptic neurotransmission is necessary for the formation of barrel columns (Li *et al*, 2013). Genetically removing 5-HT_{1B} receptors from *MAOA*- and *5-HTT*-knockout mice rescues the formation of barrel fields (Salichon *et al*, 2001), affirming that the excess extracellular 5-HT availability in *MAOA*- and *5-HTT*-knockout mice disrupts barrel field formation through 5-HT_{1B} receptor activation. Intriguingly, birth reduces extracellular 5-HT levels and this reduction is necessary and sufficient for birth to serve as an initiator for barrel formation (Toda *et al*, 2013).

Too little 5-HT can also pose problems for barrel field formation. Lesioning 5-HT fibers on the day of birth leads to a 20–30% decrease in the size of barrels at P6 and P60 (Bennett-Clarke *et al*, 1994), and depleting 5-HT in neonatal pups with the toxin p-chloroamphetamine decreases the number of 5-HTergic axons in the barrel field, and delays the segmentation of thalamocortical projections into individual barrels (Blue *et al*, 1991). *VMAT2*-knockout mice, which have virtually undetectable levels of 5-HT, DA and norepinephrine (NE) in the brain, also show a lack of barrel formation in SSC; however, thalamocortical axons segregate properly, with a 1-day delay. This dissociation between the effects of VMAT2 deficiency on layer IV barrels and thalamocortical axons indicates that monoamines are essential for the formation of barrels in the cortex, but not for thalamocortical axon patterning (Alvarez *et al*, 2002).

5-HT and Visual System Development

In rodents, crossed and uncrossed retinal fibers have a distinct pattern of distribution within the superior colliculus (SC) and the lateral geniculate nucleus (LGN; Reese and Cowey, 1983). This adult pattern is due to spontaneous activity within retinal cells, as well as competition between inputs from the two eyes. Blocking neural activity in one eye prevents normal pattern formation in the SC (Thompson and Holt, 1989), and blocking activity in the target region disrupts pattern development within the LGN (Shatz and Stryker, 1988). In mammals, retinal axons initially innervate the contralateral and ipsilateral LGN in an intermingled fashion. Over a critical period spanning from approximately P3 to P8, ipsilateral and contralateral retinal axons become organized into a predictable layer-dependent pattern of distribution through gradual pruning of inappropriate projections and expansion of correct projections in retinothalamic axons (Sretavan and Shatz, 1986).

Increased 5-HT disrupts normal pattern development in the SC of the Syrian hamster (Mooney *et al*, 1998), and *MAOA*-knockout mice show a failure of crossed and uncrossed retinal fibers to segregate in the LGN and the SC (Upton *et al*, 1999). This disrupted pattern can be rescued by inhibiting 5-HT synthesis during the first 2 weeks of life (Upton *et al*, 1999). During this 2-week period, retinal fibers transiently express *5-HTT*, *VMAT2*, and *HTR1B* (Hansson *et al*, 1998; Lebrand *et al*, 2006; Upton

et al, 2002; Upton *et al*, 1999). Therefore, a similar mechanism is proposed for the 5-HT-mediated alteration in pattern development in somatosensory and visual systems. Transient *5-HTT* expression keeps extracellular 5-HT below a critical concentration. An excess of extracellular 5-HT such as seen in *5-HTT*- or *MAOA*-knockout mice activates 5-HT_{1B} receptors on thalamocortical or retinogeniculate axon terminals, thereby decreasing their excitatory glutamatergic output (Rhoades *et al*, 1994) and disrupting the activity-dependent maturation of axon collaterals necessary for the segregation of SC and LGN inputs. Interestingly, a lack of 5-HT or 5-HT_{1B} receptors affects the refinement of the SC retinal projection, whereas the establishment of eye-specific patterns in the dorsal LGN appears not to be sensitive (Upton *et al*, 2002). But as observed for barrel field formation, birth-induced reduction of extracellular 5-HT levels regulates the segregation of retinal ganglion cell axons to the LGN (Toda *et al*, 2013).

Functional Consequences

5-HTT $-/-$ mice display reduced cerebral glucose utilization in response to whisker stimulation across all levels of somatosensory whisker processing (Esaki *et al*, 2005), a deficit that is rescued by the administration of the 5-HT synthesis inhibitor parachlorophenylalanine (PCPA). Behavioral deficits that could result from somatosensory or visual system dysfunction include prolonged righting and trembling during locomotion seen in MAOA-deficient pups (Cases *et al*, 1995) and motor deficits seen in both MAOA- and 5-HTT-deficient adult mice (Bortolato *et al*, 2013; Cases *et al*, 1995; Morelli *et al*, 2011); however, proof of a causal relationship is thus far lacking.

Clinical Relevance

High levels of 5-HT during a sensitive perinatal period cause permanent anatomical defects in the somatosensory and visual system. The underlying mechanisms likely apply to other systems as well, because transient expression of *5-HTT* also occurs in other sensory, thalamic, hippocampal, hypothalamic, and prefrontal cortical neurons throughout development in rodents (Lebrand *et al*, 1996; Lebrand *et al*, 1998; Narboux-Neme *et al*, 2008). Transient ectopic *5-HTT* expression during development is also observed in non-human primates, eg, in sensory neurons of the common marmoset (Lebrand *et al*, 2006). In human 12 to 14-week-old fetuses, 5-HTT-immunolabeled fibers have been identified in the rostral and caudal limbs of the internal capsule, including putative thalamocortical fibers that project from the mediodorsal thalamus to the frontal cortex (Verney *et al*, 2002). Thus, humans and rodents may share a similar role for 5-HT and 5-HT uptake during cortical development. The hypothesized conservation of ectopic *5-HTT* expression in humans is of interest because it might relate not only to sensory phenotypes but also to clinical psychopathology.

Many psychiatric and neurodevelopmental disorders, including autism spectrum disorder, attention deficit hyperactivity disorder, developmental coordination disorder, and schizophrenia encompass sensory and/or motor deficits (Butler *et al*, 2001; Crane *et al*, 2009; Dewey *et al*, 2007; Doniger *et al*, 2002; Piek and Dyck, 2004; Rogers and Ozonoff, 2005). Symptoms vary broadly, manifesting as sensory hypo- or hyper-responsiveness, or problems with sensory filtering. The presence of sensory symptoms in these disorders that are primarily characterized by emotional and cognitive dysfunction supports the hypothesis of common mechanisms underlying sensory/motor and emotional/cognitive phenotypes.

A 5-HT-SENSITIVE DEVELOPMENTAL PERIOD IMPACTING ADULT EMOTIONAL BEHAVIOR AND COGNITION

Though limbic circuits retain some plasticity in adult life, their formation and interconnectivity is predominantly set during embryonic and postnatal development. Heightened plasticity during circuit development bestows malleable potential to environmental and genetic factors (Hensch, 2004; Knudsen, 2004). Hence, much like the maturation of sensory systems, limbic circuit formation may also pass through sensitive developmental periods, during which external and internal factors can impact and modulate circuit formation and consequently, behaviors encoded by them. Such a model is congruent with mood disorders often having their origins in early life (Baram *et al*, 2012; Caspi *et al*, 2003; Kendler *et al*, 1992; Moffitt *et al*, 2007; Pietrek *et al*, 2013; Quinn *et al*, 2013; Wals and Verhulst, 2005). Although our understanding of the molecular factors that define maturing limbic circuit properties is still limited, 5-HT has emerged as one such factor modulating not only adult limbic function, but also limbic circuit formation.

5-HT and Emotional and Cognitive Behavior

5-HT signaling modulates emotional behavior (Arango *et al*, 2003; Charney, 1998; Fernandez and Gaspar, 2012). Reduced plasma and platelet 5-HT levels as well as blunted prefrontal cortical responses to elevated 5-HT are observed in psychopathological states such as depression, panic disorders, and post-traumatic stress disorder (Anderson *et al*, 2004; Cannon *et al*, 2013; Davis *et al*, 1997; Kovacic *et al*, 2008; Lesch *et al*, 1996; Maron *et al*, 2004; Spivak *et al*, 1999). Manipulations evoking hypo-5-HTergic states such as tryptophan depletion exert prodepressive effects (Blokland *et al*, 2002; Feder *et al*, 2011), whereas selective 5-HT reuptake inhibitors (SSRIs) that block the 5-HTT and hence enhance synaptic 5-HT levels have antidepressant and anxiolytic efficacy (Fuller and Wong, 1990). Preclinical research mirrors this relationship, as reduced firing of 5-HTergic neurons is often observed in animal models of depression and anxiety (Bambico *et al*, 2009; Challis *et al*, 2013). Although genome-wide association studies (GWAS)

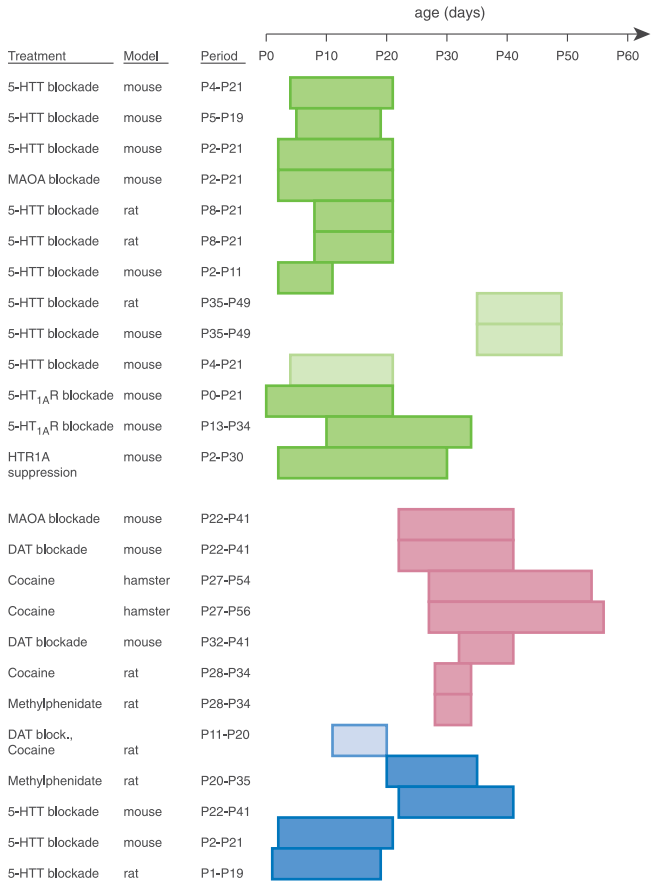
have thus far not identified genetic risk loci for depression (Flint and Kendler, 2014), the relationship between perturbed 5-HTergic signaling and affective behavior is further supported by genetic linkage and association studies. Congruent with the generally positive correlation of 5-HTergic phenotypes and emotion, low-expressing alleles of *TPH2* coding for the 5-HT-synthesizing enzyme tryptophan hydroxylase 2 (Gutknecht *et al*, 2007; Reuter *et al*, 2007; Zill *et al*, 2004) and the high-expressing variant of the presynaptic inhibitory receptor *HTR1A* (Lemonde *et al*, 2003; Schmitz *et al*, 2009) are associated with negative emotionality and enhanced predisposition to depression and suicidality. However, polymorphisms in the regulatory regions of MAOA, which negatively influence its transcriptional levels (Sabol *et al*, 1998), are also associated with enhanced anxiety and depressive behavior (Schmidt *et al*, 2000; Tadic *et al*, 2003). Likewise, the hypomorphic short (*s*) allelic variant of the *5-HTT* gene-linked polymorphic region (5-HTTLPR) is associated with trait anxiety and 'neuroticism', and increased susceptibility to environmental stress in some (Grabe *et al*, 2012; Lesch *et al*, 1996; Xie *et al*, 2009), albeit not all studies (Fisher *et al*, 2012; Peyrot *et al*, 2013). These surprising associations are in line with reduced expression of 5-HTT found in brains of depressed individuals and suicide victims (Underwood *et al*, 2012; Willeit *et al*, 2000). Anxiogenic associations with hypomorphic *MAOA* and *5-HTT* alleles are opposite to what one would predict based on the anxiolytic and antidepressant effects of monoamine oxidase inhibitors and drugs blocking the 5-HTT (Fuller and Wong, 1990). However, pharmacological treatments usually circumvent developmental periods, whereas genetic factors act throughout life, including development. Hence, these results suggest that elevated 5-HT levels may exert starkly contrasting effects on emotional behavior, depending upon the age of exposure.

Both non-human primate and rodent models support a central role for 5-HTergic genotypes in establishing psychiatric vulnerability. MAOA-deficient mice exhibit enhanced startle behavior and decreased exploration of novel environments (Cases *et al*, 1995; Chen *et al*, 2004). These behavioral phenotypes correlate with increased monoamine levels specifically in postnatal life, as the gradual rise in monoamine oxidase B (MAOB) normalizes adult monoamine metabolism (Tsang *et al*, 1986). Whereas MAOA activity impacts 5-HT, DA, and NE levels, 5-HTT function selectively regulates 5-HT signaling. In *5-HTT* $-/-$ mice, elevated extracellular 5-HT correlates with enhanced anxiety, learned helplessness, behavioral despair, and impaired social interaction (Ansorge *et al*, 2004; Kalueff *et al*, 2007; Lira *et al*, 2003; Moy *et al*, 2009; Muller *et al*, 2011). *5-HTT*-knockout animals also exhibit impaired extinction recall of fearful memories (Wellman *et al*, 2007). Loss-of-function and hypomorphic *5-HTT* variants also enhance the susceptibility to adverse behavioral effects of stressors. Rhesus macaques carrying an orthologue of the *5-HTT s* allele and *5-HTT* $-/-$ mice exhibit exaggerated behavioral and neuroendocrine responses to mild stress, particularly when also exposed to early-life stress (Adamec *et al*, 2006; Jiang *et al*, 2009). Resembling the phenotype of 5-HTT-deficient mice, loss of all or only presynaptic inhibitory 5-HT_{1A} receptors results in increased anxiety-related behaviors (Gross *et al*, 2002; Heisler *et al*, 1998; Parks *et al*, 1998; Ramboz *et al*, 1998; Richardson-Jones *et al*, 2011).

Indicating a linear relationship between developmental 5-HT tone and adult emotional behavior, multiple transgenic models of life-long hypo-5-HTergic function, including those defective in raphe specification (*LMX1b-PET1Cre, PET1-Tox, PET1* $-/-$), 5-HT packaging (*VMAT2-SERTCre*), or exhibiting enhanced reuptake of synaptic 5-HT (*5-HTT*-overexpressing mice), display enhanced exploration of novel environments and reduced innate anxiety (Dai *et al*, 2008; Jennings *et al*, 2006; Kiyasova *et al*, 2011a; Narboux-Neme *et al*, 2011). However, some constitutive mutants for genes involved in 5-HTergic fate specification (*PET1* $-/-$) and synthesis (*TPH2* $-/-$) with drastically reduced 5-HT levels exhibit prodepressive and anxiogenic behavior (Beaulieu *et al*, 2008; Hendricks *et al*, 2003). Hence, a simple linear relationship breaks apart at extreme ends, suggesting that both severe depletion and elevation of 5-HT during development adversely influences adult emotional behaviors, but still supporting the core hypothesis that developmental 5-HT signaling establishes the set point for adult emotionality.

Direct proof of this hypothesis requires temporal control over 5-HTergic parameters, which constitutive genetic models lack. Pharmacologic probing of the 5-HTsystem during development lacks 100% target specificity but has nevertheless proven invaluable in advancing our knowledge of 5-HT-sensitive periods (Table 1). For example, animals administered SSRIs or 5-HTT blocking tricyclic antidepressants during the first 3 weeks of postnatal life (P4–P21), but not in adulthood (P90–P107 or P56–P70), mimic the prodepressive and anxiogenic phenotype observed in transgenic models with constitutively enhanced 5-HTergic tone (Ansorge *et al*, 2004, 2008; Popa *et al*, 2008). We have recently refined this SSRI-sensitive period to P2–P11, and extended the behavioral characterization, finding impaired hippocampal-dependent spatial learning and contextual fear learning, as well as diminished amygdala and PFC-dependent fear extinction and extinction recall (Rebello *et al*, 2014). This P2–P11 period, interestingly, not only lies within the maturation period of both 5-HTergic afferents and cortical circuits (Kiyasova and Gaspar, 2011b; Lidov and Molliver, 1982a; Lidov and Molliver, 1982a; Vitalis *et al*, 2013), but also coincides with the peak of cortical 5-HT and 5-HT metabolite levels (Hohmann *et al*, 1988; Figure 1). Such tight confinement of this sensitive period, however, does not persist when comparing between species. For example, although in mice, PA SSRI exposure lacks persistent consequences on fear-, anxiety-, or stress-related behaviors (Norcross *et al*, 2008; Yu *et al*, 2014), rats exhibit increases in anxiety-like behavior following P25–P46, P35–P49, or P67–P88 5-HTT blockade (Iniguez *et al*, 2010, 2014;

TABLE 1 Consequences of Transient Monoaminergic Interference on Adult Behavior



Treatment	Model	Period	Adult behavioral consequence	Tests Used	Reference
5-HTT blockade	mouse	P4-P21	increased anxiety/depression-like	OF, EPM, NSF, SE	Ansorge et al, 2004; Ansorge et al, 2008
5-HTT blockade	mouse	P5-P19	increased depression-like	LD, EPM, SP,	Popa et al, 2008
5-HTT blockade	mouse	P2-P21	increased anxiety/depression-like	OF, NSF, SE	Yu et al, 2014
MAOA blockade	mouse	P2-P21	increased anxiety/depression-like; no effect on aggression	OF, NSF, SE; IIA	Yu et al, 2014
5-HTT blockade	rat	P8-P21	increased depression-like	OFT, ICSS	Vogel et al, 1990
5-HTT blockade	rat	P8-P21	increased depression-like	FST	Hansen et al, 1997
5-HTT blockade	mouse	P2-P11	increased anxiety/ depression-like	OF, EPM, NSF, SE, FST	Rebello et al, 2014
5-HTT blockade	rat	P35-P49	increased anxiety; decreased depression-like	EPM, NSF; FST, SP	Iniguez et al, 2010
5-HTT blockade	mouse	P35-P49	increased anxiety; decreased depression-like	EPM; FST, SD	Iniguez et al, 2014
5-HTT blockade	mouse	P4-P21	increased anxiety; decreased depression-like	LD, OF; FST	Karpova et al, 2009
5-HT_{1A}R blockade	mouse	P0-P21	increased anxiety	OFT, EPM	Vinkers et al, 2010
5-HT_{1A}R blockade	mouse	P13-P34	increased anxiety	OF, NSF	Lo Iacono et al, 2008
HTR1A suppression	mouse	P2-P30	increased anxiety	OF, EPM	Donaldson et al, 2014
MAOA blockade	mouse	P22-P41	increased aggression and AMPH resp; normal anxiety/depression-like	IIA, OF; OF, NSF, SE	Yu et al, 2014
DAT blockade	mouse	P22-P41	increased aggression and AMPH resp.	IIA	Yu et al, 2014
Cocaine	hamster	P27-P54	increased aggression (not adult, @ P55)	RI	Harrison et al, 2000
Cocaine	hamster	P27-P56	increased aggression (not adult, @ P57)	RI	DeLeon et al, 2002
DAT blockade	mouse	P32-P41	increased aggression and AMPH resp.	IIA, OF	personal communication MSA
Cocaine	rat	P28-P34	increased cocaine response	OF	Brandon et al, 2001
Methylphenidate	rat	P28-P34	increased cocaine response	OF, CSA	Brandon et al, 2001
DAT block., Cocaine	rat	P11-P20	reduced and increased DAergic challenge responses	OF	Dow-Edwards and Busidan, 2001
Methylphenidate	rat	P20-P35	reduced cocaine response and CPP	OF, PC	Andersen et al, 2002
5-HTT blockade	mouse	P22-P41	reduced aggression and AMPH resp.	IIA	Yu et al, 2014
5-HTT blockade	mouse	P2-P21	reduced aggression	IIA	Yu et al, 2014
5-HTT blockade	rat	P1-P19	reduced aggression	SIA	Manhaes De Castro 2011

Abbreviations: CSA, cocaine self administration; EPM, elevated plus maze; FST, forced swim test; ICSS, intracranial self stimulation; IIA, isolation-induced aggression test; LD, light dark box test; NSF, novelty-suppressed feeding test; OF, open field test; PC, place conditioning; RI, resident–intruder test; SD, social defeat test; SE, shock escape test; SIA, shock-induced aggression; SP, sucrose preference test; TST, tail suspension test.
Dark green indicates increased anxiety/depression-like behavior. Light green indicates increased anxiety but decreased depression-like behavior. Red indicates increased aggression/behavioral stimulant response, dark blue indicates reduced aggression/behavioral stimulant response, light blue indicates mixed behavioral DAergic challenge response.

Karpova *et al*, 2009). Likewise, although in mice, 5-HTT blockade between P2 and P11 impairs cognitive behavior (Rebello *et al*, 2014), pharmacological perturbations that enhance levels of 5-HT from P11 to P20 but not from P1 to P10 result in dose-related impairments of sequential learning and spatial learning and memory in rats (Broening *et al*, 2001; Morford *et al*, 2002). These findings suggest that 5-HT-sensitive periods exhibit species-specific characteristics. Furthermore, specific behavioral phenotypes resulting from postnatal SSRI treatment appear to exhibit differential sensitivity to the timing of SSRI treatment. Interestingly, both rat and mouse studies have revealed timing-dependent bidirectional effects of chronic 5-HTT blockade. Although clomipramine or SSRI exposure in rats from P8 to P21 causes enhanced immobility in the forced swim test (Hansen *et al*, 1997; Vogel *et al*, 1990); PA (P35–P49), but not adult (P65–P79), fluoxetine (FLX) exposure reduces floating (Iniguez *et al*, 2010). In mice, P2–P11 FLX exposure increases forced swim test immobility (Rebello *et al*, 2014), whereas P4–P21 or P35–P49 FLX exposure reduces floating (Iniguez *et al*, 2014; Karpova *et al*, 2009).

Importantly, developmentally blocking the other two major brakes of 5-HT signaling, MAOA and 5-HT_{1A} autoreceptors, results in comparable behavioral sequelae, but again, some differences exist with regard to timing (Table 1). The refined 5-HTT blockade sensitive period (P2–P11) overlaps with the MAOA blockade sensitive period (P2–P21; Yu *et al*, 2014), but dissociates from the 5-HT_{1A} receptor blockade sensitive period (Donaldson *et al*, 2014; Gross *et al*, 2002; Lo Iacono and Gross, 2008; Richardson-Jones *et al*, 2011; Vinkers *et al*, 2010). Pharmacological 5-HT_{1A} receptor blockade from P0 to P21 (Gross *et al*, 2002; Vinkers *et al*, 2010) or P13 to P34 (Lo Iacono and Gross, 2008), is sufficient to elicit the adult anxiety phenotype. Furthermore, the suppression of endogenous *HTR1A* autoreceptor expression throughout life or from P2 to P30 is sufficient to increase anxiety in the adult (Donaldson *et al*, 2014; Richardson-Jones *et al*, 2011).

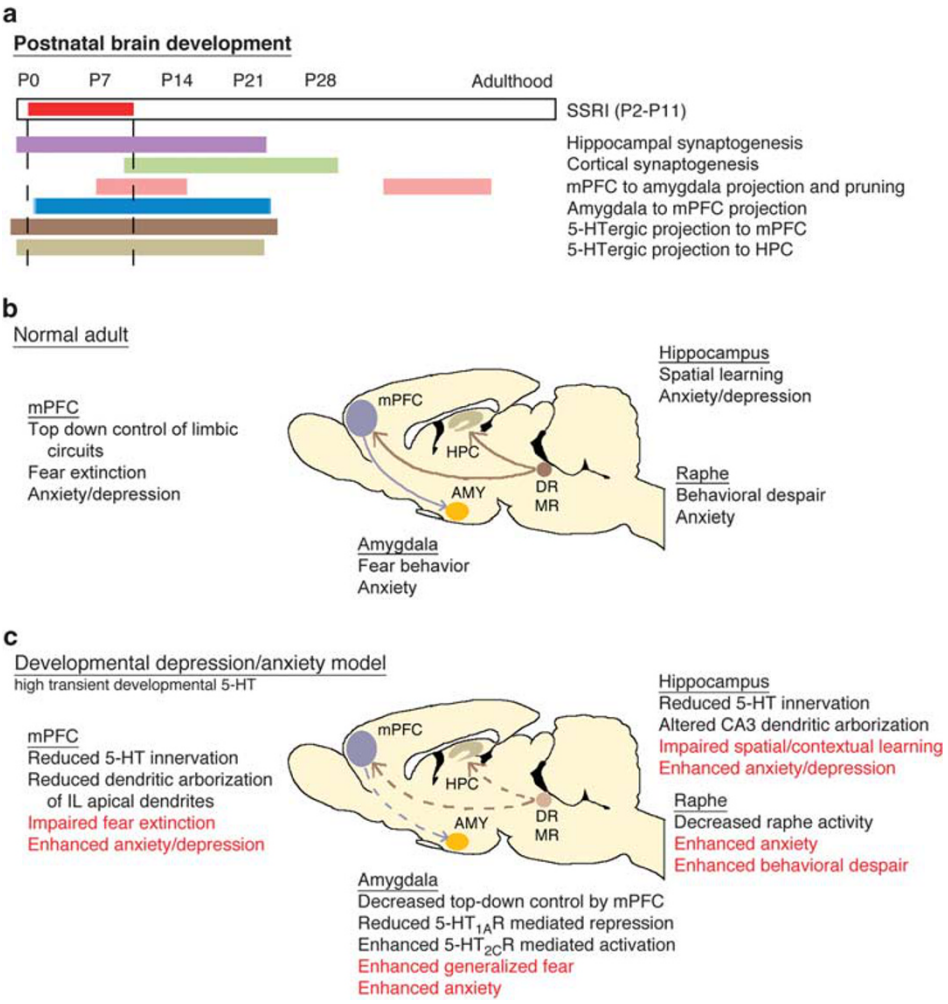


Figure 2. The 5-HT-sensitive developmental period—neural correlates of behavioral sequelae. (a) Diagram of critical developmental processes that overlap temporally with early postnatal SSRI treatment (P2–P11). Due to the temporal overlap, these processes provide candidate mechanistic underpinnings of early postnatal SSRI-induced alterations in affective behaviors. (b) Key nodes involved in anxiety and depressive behaviors and their basic functions and connectivity in the normal adult brain. (c) Summary of alterations occurring within the key nodes of the circuit as a result of developmental 5-HT elevation, and the resulting anxiety and depressive behaviors seen during adulthood. AMY, amygdala; mPFC, medial prefrontal cortex; HPC, hippocampus; DR, dorsal raphe nucleus; MR, median raphe nucleus; IL, infralimbic cortex; SSRI, selective 5-HT reuptake inhibitor; 5-HT, serotonin.

Overall, even with the species and target effects taken into account, the convergence of behavioral malleability when interfering with 5-HT signaling during early postnatal periods highlights the importance of this time window for circuit maturation and circuit plasticity.

Mechanistic Insight on the Postnatal Establishment of Perturbed Emotionality

Elevated postnatal 5-HT levels may exert their effects by impinging on the normal developmental trajectory of both its target limbic neurocircuits as well as the 5-HTergic system itself. For example, the autoinhibitory effect of 5-HT on 5-HTergic differentiation reduces 5-HT neuronal numbers in embryonic raphe cultures (Rumajogee *et al*, 2004) and *5-HTT* −/− mice (Lira *et al*, 2003). Though these changes might carry their own behavioral consequences, they likely dissociate from the effects produced by increased early postnatal 5-HT signaling, because 5-HTergic cell numbers are set at that time point. However, additional aspects of 5-HTergic function are still malleable during postnatal periods (Figure 2). 5-HTergic neurons of the dorsal raphe fire at a fourfold lower rate in *5-HTT* −/− mice when compared with controls (Lira *et al*, 2003). Likewise, rats exposed to clomipramine from P8 to P21 and mice exposed to FLX from P4 to P21 also have reduced 5-HTergic neuronal activity when compared with vehicle-treated controls in adulthood (Kinney *et al*, 1997; personal communication MSA). Furthermore, 5-HTergic fiber density in the HPC and medial PFC (mPFC) of rats treated with citalopram (Maciag *et al*, 2006; Weaver *et al*, 2010) or mice treated with FLX (personal communication MSA) during postnatal development is reduced. These anatomical abnormalities might synergize with hypo-5-HTergic tone to

weaken functional connectivity and thus 5-HTergic modulation of the HPC and mPFC, which in turn could underlie increased anxiety/depression and impaired cognition. Testing of such direct causal relationships between circuit-specific 5-HTergic input and behavior are underway in many labs that are applying optogenetic and pharmacogenetic tools to decipher the 5-HTergic code *in vivo*. For example, a recent study has uncovered a role for 5-HT in encoding reward, wherein the enhanced activity of dorsal raphe neurons is observed in reward-associated tasks, and optogenetic manipulation of 5-HTergic neuronal activity strongly biases reward-associated behaviors (Liu *et al*, 2014).

In addition to autoregulation, 5-HT acts via 14+ heteroreceptors located on a vast and diverse population of postsynaptic target cells. With these heteroreceptors emerging early in development, it is likely that enhanced levels of early postnatal 5-HT act via heteroreceptors to influence postsynaptic circuit maturation thus evoking structural, physiological, and behavioral consequences. Several specific 5-HT heteroreceptors have emerged as potential candidates in mediating 5-HT-sensitive period consequences. For example, 5-HT_{2A} receptors in the forebrain have a key role in the regulation of anxiety behavior, as their constitutive ablation reduces conflict anxiety (Weisstaub *et al*, 2006). As adult treatment with 5-HT_{2A} antagonists fails to evoke similar anxiolytic effects (Griebel *et al*, 1997; Kehne *et al*, 1996), the *HTR2A −/−* phenotype might have developmental origins. Conversely, increased 5-HT_{2A} receptor signaling during development would be predicted to exert anxiogenic consequences in adulthood. Indeed, postnatal blockade of the 5-HT_{2A} and 5-HT_{2C} receptors prevents the emergence of early SSRI-evoked anxiety and depressive behavior (Sarkar *et al*, 2013). The dynamic developmental expression characteristics of cortical *HTR2A* further support a causal role for this particular receptor in mediating the effects of early postnatal 5-HTT blockade: the shift of cortical neuron responses to 5-HT, from 5-HT_{2A}-mediated excitation in early postnatal life to predominantly inhibitory responses past P15 could explain the extent of the murine 5-HTT sensitive period (Beique *et al*, 2004; Zhang, 2003).

5-HT_{3A} receptors have been invoked as critical mediators of developmental 5-HT signaling through studies of cortical cytoarchitecture. Postnatal FLX treatment reduces the arborization of apical dendrites of layer 2/3 infralimbic (IL) but not prelimbic (PL) pyramidal neurons in mice (Rebello *et al*, 2014; Figure 2). A similar 5-HT sensitivity has been reported for layer 2/3 pyramidal neurons in the SSC, where increased 5-HT signaling from E8 to E18 decreases apical dendritic arborization (Chameau *et al*, 2009; Smit-Rigter *et al*, 2012). This latter effect is mediated by 5-HT_{3A} receptors present on reelin secreting Cajal–Retzius cells (Smit-Rigter *et al*, 2012), which upon activation stimulate the release of reelin, which in turn limits cortical neuron apical dendritic elaboration (Chameau *et al*, 2009; Smit-Rigter *et al*, 2011). As Cajal–Retzius cells are still present and active in the first two postnatal weeks, a similar mechanism involving hyperactivation of the 5-HT_{3A}receptors can be postulated for the cytoarchitectural changes observed following postnatal FLX treatment. Differential activity or sensitivity of this pathway as a function of time and region might underlie the restriction of postnatal SSRI consequences to the apical arbors of IL and not PL neurons. An interesting, yet unstudied, aspect in that regard is whether developmental 5-HT signaling permanently impacts the cytoarchitecture and consequently function of Cajal–Retzius cells themselves and/or other *HTR3A* expressing interneurons such as neurogliaform cells.

5-HT_{1B} receptors are also strong candidates for mediating the effects of excessive early-life 5-HT on cytoarchitecture. The critical role of 5-HT_{1B} receptors in shaping sensory system development can be hypothetically transposed to the maturation of non-sensory thalamocortical connectivity and cortical architecture, as well as hippocampal wiring. Neurons of the thalamic medial dorsal nucleus that project to the mPFC and influence pyramidal cell dendritic arborization (Marmolejo *et al*, 2012), express high levels of *HTR1B* (Bonnin *et al*, 2006), *5-HTT*, and *VMAT2* in early postnatal life (Lebrand *et al*, 1998). Therefore, 5-HT could act through 5-HT_{1B} receptors to modulate the activity of thalamocortical afferents projecting to the PFC and thus influence thalamocortical axonal fields and cortical cytoarchitecture, thereby contributing to the postnatal SSRI-induced structural changes in the PFC.

Taken together, current preclinical data allow us to conclude that increased extracellular 5-HT during P2–P11, regardless of the primary cause, elicits adult anxiety and depression-like behavior and impairs cognition in rodents. Mechanistic studies highlight that 5-HT receptor diversity results in pleiotropic effects of 5-HT during development to elicit these long-lasting changes in emotional and cognitive behavior (Figure 2). Most mechanistic insight has related specific receptors to specific neuroanatomical and neurophysiological phenotypes. How such phenotypes relate to adult behavior remains to be established for most cases. Optogenetic and pharmacogenetic techniques have proven invaluable for testing causal relationships between neurophysiology and behavior. Tools to manipulate and sculpt cytoarchitecture and circuit connectivity remain to be established.

Early-Life Adversity and 5-HT Perturbation

Exposure to diverse early-life stressors including inadequate maternal care, maternal separation, and novelty exposure evoke persistent enhancements in anxiety and depression-related behaviors, altered cognitive function, and dysregulated neuroendocrine responses to adult stressors (Kalinichev *et al*, 2002; Lehmann *et al*, 1999; Suri *et al*, 2013). Concomitantly, early-life adverse experience evokes 5-HTergic dysregulation in mice. For example, early-life stress exposure increases postnatal 5-HT and 5-HT metabolite levels in the dorsal raphe and its limbic projection areas, the amygdala, the HPC, and the mPFC (Franklin *et al*, 2011;

Ohta *et al*, 2014; Raftogianni *et al*, 2012; Rentesi *et al*, 2013), and reduces dorsal raphe *HTR1A* expression and 5-HT_{1A} receptor levels (Leventopoulos *et al*, 2009; Ohta *et al*, 2014), together strongly indicative of a postnatal hyper-5-HTergic phenotype. Furthermore, maternal separation increases prefrontal 5-$HT_{2A/2C}$ receptor function during the second postnatal week (Benekareddy *et al*, 2010) and blockade of 5-$HT_{2A/2C}$ function during maternal separation prevents the emergence of the adverse early stress-evoked behavioral and molecular sequelae (Benekareddy *et al*, 2011). Together, these findings strongly indicate that early-life stress acts through early postnatal 5-HT-sensitive period interference to impact adult behavior.

If this model is broadly applicable, then early-life stress should interact with genetic factors that also alter 5-HT signaling to confer risk for later life emotional dysfunction. Indeed, some studies indicate that 5-HTT genotypes interact with life history to determine adult vulnerability to psychopathology: eg, individuals carrying the *s* allele are more likely to suffer from depression only in the background of stressful life history, and in particular when adverse early events were experienced (Caspi *et al*, 2003; Grabe *et al*, 2012; Xie *et al*, 2009). All positive candidate gene linkage and association studies for major depression and related disorders have come under criticism, because GWAS have so far failed to independently identify risk alleles (Flint and Kendler, 2014). However, because the study of human environmental factors, as well as insight gained through the work on non-human primate and rodent models, converge to highlight the importance of developmental 5-HT, we predict that GWAS will eventually detect genetic risk factors which likewise impinge on developmental 5-HT signaling.

Clinical Relevance

Basic research has strongly shaped the model in which maturing 5-HTergic input during developmental periods has an instructive role in the maturation of limbic neurocircuits, and dysregulation of 5-HTergic signaling impinges on normal development to evoke persistent changes in emotionality. Early human studies investigating this relationship have focused greatly on the *5-HTTLPR* variants, and their role in psychopathology, with many but not all studies reporting an association between the low-expressing *s* allele and increased trait anxiety (Lesch *et al*, 1996; Schinka *et al*, 2004; Sen *et al*, 2004), increased incidence and severity of major depressive disorder following a stressful life event (Caspi *et al*, 2003; Culverhouse *et al*, 2013; Karg *et al*, 2011; Munafo *et al*, 2009; Risch *et al*, 2009; Zalsman *et al*, 2006), and heightened behavioral reactivity to fearful stimuli (Armbruster *et al*, 2009; Brocke *et al*, 2006). A common *5-HTT*-polyadenylation polymorphism reducing 5-HTT expression is associated with fear extinction recall deficits (Hartley *et al*, 2012; Yoon *et al*, 2013).

Consistent with these behavioral data, brain imaging studies demonstrate an association between the *s* allele and higher levels of amygdala activation in response to fearful stimuli (Furmark *et al*, 2004; Hariri *et al*, 2002; Kobiella *et al*, 2011; Murphy *et al*, 2013; Scharinger *et al*, 2010), reduced grey matter volumes in the dorsolateral PFC, amygdala and the HPC (Atmaca *et al*, 2011; Frodl *et al*, 2008; Kobiella *et al*, 2011; Pezawas *et al*, 2005), microstructural changes in the uncinate fasciclus, a white matter tract connecting limbic and frontal areas, including the amygdala and anterior cingulate cortex (Pacheco *et al*, 2009), and decreased coupling of the amygdala-anterior cingulate circuit (Heinz *et al*, 2005; Lemogne *et al*, 2011; Pezawas *et al*, 2005; Roiser *et al*, 2009; Shah *et al*, 2009; Volman *et al*, 2013). Importantly, functional coupling between the anterior cingulate cortex and the amygdala is correlated with trait anxiety (Hahn *et al*, 2011; Prater *et al*, 2013).

Although the influence of the *5-HTTLPR* on promoter activity and the production of mRNA, protein product, and 5-HT reuptake activity has been documented in cellular assays (Bradley *et al*, 2005; Heils *et al*, 1996; Lesch *et al*, 1996; Philibert *et al*, 2008; Stoltenberg *et al*, 2002), paradoxically nearly all attempts to examine the influence of *5-HTTLPR* promoter variants on 5-HTT levels in adult brain have been negative (Lim *et al*, 2006; Murthy *et al*, 2010; Oquendo *et al*, 2007; Parsey *et al*, 2006; Preuss *et al*, 2000). This disconnect leaves open the possibility of a more prominent impact of the *5-HTTLPR* on developmental 5-HTT expression, including transient *5-HTT* expression during human fetal development. Such a role would be congruent with clinical and endophenotype-related associations originating during sensitive developmental periods.

The 5-HT-sensitive murine P2–P11 period roughly corresponds to the 3rd trimester of human gestation. Consequently, preclinical findings become relevant in the context of SSRI use during pregnancy. Up to 8% of pregnant women are reported to use SSRIs, and their use during pregnancy is currently increasing (Andrade *et al*, 2008; Bakker *et al*, 2008). SSRIs cross the placental barrier (Hendrick *et al*, 2003; Rampono *et al*, 2004) and can be measured in amniotic fluid (Loughhead *et al*, 2006). Although SSRIs do not cause any overt developmental abnormalities in the neonates (Chambers *et al*, 1996; Pastuszak *et al*, 1993; Simon *et al*, 2002), *in utero* exposure to SSRIs increases the risk of preterm birth and lower birth weights (El Marroun *et al*, 2012; Grzeskowiak *et al*, 2012; Oberlander *et al*, 2006). Furthermore, an association between the use of SSRIs during pregnancy and persistent pulmonary hypertension (Chambers *et al*, 2006; Kieler *et al*, 2012), congenital cardiac defects (Berard *et al*, 2007; Diav-Citrin *et al*, 2008; Pedersen *et al*, 2009) and a slight delay in motor development (Casper *et al*, 2003; de Vries *et al*, 2013; Hanley *et al*, 2013) have been noted in the neonates. Exposed infants also display indications of central nervous system stress at 3 weeks after birth (Salisbury *et al*, 2011), and affected neurological functioning as measured by general movement at 3–4 months postpartum (de Vries *et al*, 2013). Symptoms appear to be moderated by infant *5-HTTLPR*, as infants

homozygous for the *s* allele display higher severity of symptoms (Oberlander *et al*, 2008), reinforcing the hypothesis that a high level of 5-HT during development is detrimental. To date, little is known about the long-term impact of *in utero* SSRI exposure on brain development, adult behavior, and the prevalence of emotional disorders later in life. Recent studies have suggested enhanced internalizing behavior in childhood (Oberlander *et al*, 2010), and an increased risk of autism spectrum disorders in prenatally SSRI-exposed offspring (Croen *et al*, 2011; Rai *et al*, 2013). These findings are in line with an association noted between the *5-HTTLPR* and specific deficits observed in autism spectrum disorders, whereby those possessing the *s* allele demonstrate higher deficiencies in nonverbal and social behaviors (Brune *et al*, 2006). Still, further research is needed to determine whether associations with SSRI exposure are causal, and to disentangle the effects of maternal depression versus maternal SSRI use on infant and childhood emotional behavior (Misri *et al*, 2006; Oberlander *et al*, 2010; Oberlander *et al*, 2007; Salisbury *et al*, 2011). Although small, non-population-based cohort studies observed no excess risk by age 3 to 7 (Nulman *et al*, 1997; Nulman *et al*, 2002), more longitudinal studies are required to assess the long-term effects of postnatal SSRI exposure on the development of psychiatric disorders (Malm *et al*, 2012). Ultimately, we hope that within the next 5 years, such longitudinal as well as additional epidemiological population-based studies will produce data that will allow clinicians to better weigh risks and benefits when confronted with depression during pregnancy.

A 5-HT- AND DA-SENSITIVE PERIOD IMPACTING ADULT AGGRESSION

Aggression is a behavioral construct often subdivided along defining characteristics, such as target, mode, or cause of aggression. The most frequent distinction occurs between premeditated violence, which represents a planned behavior and is associated with low autonomic response, and impulsive aggression, which is reactive and associated with high autonomic response (Barratt and Felthous, 2003; Gollan *et al*, 2005; Meloy, 2006). Adult aggression is critically regulated by monoamine signaling, 5-HT, and DA signaling in particular. These two monoamines appear to have generally opposing roles, with DA promoting and 5-HT inhibiting aggression.

DA and Aggressive Behavior

Hyperactivity of the DA system is associated with increased impulsive aggression. In animals, nucleus accumbens (NAc) DA release increases in anticipation of aggressive episodes (Ferrari *et al*, 2003; Malison *et al*, 1998), and NAc and PFC release increases during and following aggressive encounters in rats (Tidey and Miczek, 1996; van Erp and Miczek, 2000). Systemic administration of methamphetamine or the DA receptor agonist apomorphine decreases the threshold for defensive attack behavior elicited by electrical stimulation of the ventromedial hypothalamic (VMH) nucleus in cats (Maeda and Maki, 1986; Maeda *et al*, 1985). Conversely, systemic administration of the D_1/D_2 receptor antagonist risperidone (Rodriguez-Arias *et al*, 1998), the D_2 receptor antagonist raclopride (Aguilar *et al*, 1994), and the D_1 antagonist SCH23390 (Rodriguez-Arias *et al*, 1998) all reduce aggression. Furthermore, blockade of D_1 or D_2 receptors in the NAc attenuates aggression in mice (Couppis and Kennedy, 2008). Mice lacking DAT exhibit a hyper-DAergic tone, which correlates with hyper locomotion (Giros *et al*, 1996), and increased reactive aggression following mild social contact (Rodriguiz *et al*, 2004). Moreover, cocaine, which blocks the DAT, significantly escalates aggression when administered during adolescence (P27–P57; DeLeon *et al*, 2002; Harrison *et al*, 2000), and methamphetamine significantly increases aggression in male mice when administered chronically (Sokolov and Cadet, 2006; Sokolov *et al*, 2004). Heterozygous catechol-o-methyl transferase (COMT)-deficient male mice exhibit increased frontal cortex DA levels and increased aggression (Gogos *et al*, 1998). Lastly, specific activation of the VTA DAergic neuronal activity using optogenetic stimulation increases isolation-induced aggression (Yu *et al*, 2014).

Results from preclinical animal models are congruent with human studies. For example, levels of DA metabolites in the cerebrospinal fluid (CSF) of violent offenders positively correlate with psychopathy (Soderstrom *et al*, 2001). Typical and atypical antipsychotic agents that antagonize the D_2 receptor attenuate pathological aggression (Brizer, 1988; Chengappa *et al*, 1999; Dorevitch *et al*, 1999; Lenox *et al*, 1992; Lerner *et al*, 1979; Rocca *et al*, 2002; Schulz *et al*, 1999). However, low levels of D_2/D_3 receptors in the rodent NAc and decreased D_2/D_3 receptor binding in the midbrain of the human, are likewise correlated with impulsive behavior (Buckholtz *et al*, 2010b; Dalley *et al*, 2007), still highlighting the DA system but possibly suggesting compensatory adjustment. Human genetic-association studies have also linked the DA system to aggression. Among people with a diagnosis of personality disorder, the low-expressing G allele of the *COMT* rs165599 SNP is associated with self-reported aggression (Flory *et al*, 2007). Likewise, among individuals diagnosed with schizophrenia, the low-activity M*et* a*llele* of the *COMT* Val158Met polymorphism is associated with high aggression (Bhakta *et al*, 2012; Gu *et al*, 2009; Han *et al*, 2004; Hong *et al*, 2008; Koh *et al*, 2012; Kotler *et al*, 1999; Lachman *et al*, 1998; Singh *et al*, 2012; Strous *et al*, 2003; Volavka *et al*, 2004c). *DRD_2* and *DRD_4* gene variants interact to predict adolescent conduct disorder and adult antisocial behavior (Beaver *et al*, 2007), as well as dysfunctional impulsivity (Colzato *et al*, 2010), and differences in inhibitory control are associated with the *DRD_4 VNTR* polymorphism (Congdon *et al*, 2008). Collectively, these studies support the DA hypothesis of aggression, which states that DAergic hyperfunction increases aggression (de Almeida *et al*, 2005a; Seo *et al*, 2008).

5-HT and Aggressive Behavior

Hypoactivity of the 5-HT system is also correlated with increased impulsive aggression. In rats, prefrontal extracellular 5-HT declines to 80% of baseline levels during aggressive encounters (van Erp and Miczek, 2000). In rhesus macaques and vervet monkeys, levels of the 5-HT metabolite 5-hydroxyindoleacetic acid (5-HIAA) in the CSF are negatively correlated with aggression (Higley *et al*, 1992, 1996a, 1996c), risk taking (Higley *et al*, 1996b), and impulsivity (Fairbanks *et al*, 2001; Mehlman *et al*, 1994). Furthermore, manipulations that lower 5-HTergic signaling, such as PCPA injections, increase impulsivity and aggression, whereas increasing 5-HT signaling using 5-HT precursors or SSRIs can reduce aggressive behavior in rodents (Chiavegatto *et al*, 2001; Di Chiara *et al*, 1971; Hodge and Butcher, 1974; Koe and Weissman, 1966; Miczek *et al*, 2001). Pointing at a critical role for 5-HT_1 receptor subtypes in mediating the antiaggressive effects of increased 5-HT signaling, systemic administration of drugs activating 5-HT_{1A} and 5-HT_{1B} receptors exert antiaggressive effects (Bannai *et al*, 2007; Centenaro *et al*, 2008; de Boer and Koolhaas, 2005; Miczek *et al*, 1989; Olivier *et al*, 1995; Sijbesma *et al*, 1991). The link between 5-HT and aggression has been further established using genetically modified mouse models. *Pet1* knockout mice, which have an 80% reduction in the number of 5-HTergic neurons, exhibit increased aggression (Hendricks *et al*, 2003). Likewise, lifelong 5-HT depletion resulting from *TPH2* deletion (Alenina *et al*, 2009; Angoa-Perez *et al*, 2012; Mosienko *et al*, 2012) or Tph2 hypofunction (Beaulieu *et al*, 2008) increases adult aggression and impulsivity. Conversely, in mice lacking the 5-HTT, increased extracellular 5-HT is associated with reduced aggression and social approach behavior (Bengel *et al*, 1998; Holmes *et al*, 2002; Kim *et al*, 2005; Mathews *et al*, 2004; Page *et al*, 2009). Supporting the model in which 5-HT_{1B} receptor signaling exerts inhibitory control over aggressive behavior, male mice that lack 5-HT_{1B} receptors exhibit increased aggressive behavior (Brunner and Hen, 1997; Saudou *et al*, 1994; Zhuang *et al*, 1999). Finally, decreasing 5-HTergic activity during adulthood using a pharmacogenetic approach increases territorial isolation-induced aggression using the resident–intruder assay (Audero *et al*, 2013).

In humans, 5-HTergic hypofunction and impulsive aggression are also often associated. Neurochemical studies find low concentrations of CSF 5-HIAA associated with impulsivity and aggression in many cohorts (Brown *et al*, 1979, 1982; Kruesi *et al*, 1990, 1992; Linnoila *et al*, 1983; Virkkunen *et al*, 1995; Virkkunen *et al*, 1994). Several studies also report a blunted neuroendocrine and central metabolic response to a pharmacological 5-HT challenge using fenfluramine in individuals with high aggression (Coccaro *et al*, 1989, 1996, 1997b; Siever *et al*, 1999). Importantly, the endocrine response to fenfluramine challenge also inversely correlates with self-rated aggression and impulsivity in a group of healthy controls (Manuck *et al*, 1998). Conversely, SSRIs reduce impulsive aggression (Berman *et al*, 2009; Coccaro and Kavoussi, 1997a), and signaling through the 5-HT_{2A} and 5-HT_{2C} receptors exerts opposing effects on impulsive behavior, with 5-HT_{2A} antagonists reducing and 5-HT_{2C} antagonists increasing impulsivity (Krakowski *et al*, 2006; Winstanley *et al*, 2004). Furthermore, orbitofrontal 5-HT_{2A} receptor availability is increased in physically aggressive personality disorder patients (Rosell *et al*, 2010; Soloff *et al*, 2007).

Human genetic-association studies have also linked the 5-HT system to aggression. Allelic variants in the *5-HTT* and *TPH1* are associated with aggression in some studies (Davidge *et al*, 2004; Patkar *et al*, 2002; Volavka *et al*, 2004c; Winstanley *et al*, 2004), and a *TPH2* haplotype has been associated with suicidal/parasuicidal behavior and aggression scores (Perez-Rodriguez *et al*, 2010). Furthermore, the *Tyr452* allele of the *HTR2A* has been associated with childhood onset aggression (Mik *et al*, 2007). Considered together, studies support the 5-HT hypothesis of aggression, which states that 5-HTergic hypofunction increases aggression.

A Developmental Role for 5-HT and DA in Regulating Aggressive Behavior

Although many principal roles of 5-HT and DA signaling in modulating aggression have been established, many seemingly paradoxical experimental results reveal the divergent consequences of manipulating levels of these neurotransmitters as a function of time. For example, unlike the anxiolytic effects of pharmacologic MAOA inhibition in adulthood, constitutive loss-of-function mutations of *MAOA* result in a syndrome characterized by antisocial/aggressive behavior in humans (Brunner *et al*, 1993). Consistently, mice with genetic inactivation of *MAOA* (*MAOA* $-/-$) exhibit not only neophobia but also heightened levels of aggression (Cases *et al*, 1995; Godar *et al*, 2010; Scott *et al*, 2008). The divergent effects of genetic (lifelong) mutations versus pharmacologic inhibition (during adulthood) suggest that perturbed monoamine signaling during sensitive periods of brain maturation differentially modulates adult aggression. Several studies now support this hypothesis (Table 1). For instance, adult aggressive behavior is sensitive to PA (P22–P41) DA- and 5-HT manipulations (Yu *et al*, 2014). Specifically, transient MAOA and DAT blockade during PA mimics the adult hyperaggressive phenotype found in MAOA-deficient mice, whereas transient postnatal (P2–P21) or adult (P180–P201) MAOA blockade does not impact adult aggressive behavior. These temporal characteristics establish the existence of a sensitive period. Interestingly, 5-HTT blockade during that same PA period mimics the adult hypoaggressive phenotype found in 5-HTT-deficient mice, suggesting that a common underlying developmental process is modulated bidirectionally through DA and 5-HT. These findings can explain the increased aggression seen in constitutive *MAOA*, *DAT*, and *COMT* loss-of-function mouse lines (Cases *et al*, 1995;

Gogos *et al*, 1998; Rodriguiz *et al*, 2004; Scott *et al*, 2008), and also support a developmental mechanism for the low-aggression phenotype of *5-HTT −/−* mice (Holmes *et al*, 2002).

PA monoaminergic manipulations also alter the behavioral response to amphetamine challenge in adulthood, with transient MAOA or DAT blockade increasing, and transient 5-HTT blockade reducing locomotor activity after amphetamine challenge (Yu *et al*, 2014) (Table 1). Because altered amphetamine response is an indication for altered DAergic function, and with the causal link between VTA activity and aggression established, these data indicate that PA monoamine signaling permanently impacts the DAergic system, setting its activity/sensitivity and thereby determining baseline aggression levels. Whether this model of causal relationships applies or whether altered aggression and altered amphetamine response are independent consequences of interfering with adolescent monoamine signaling remains to be established.

Intriguingly, transient pharmacological DAT blockade from P11 to P20 and P20 to P35 in rats has the opposite effect on the behavioral response to stimulant exposure in adulthood, diminishing the locomotor response to cocaine challenge, while transient methylphenidate exposure during adulthood does not alter the motor response to cocaine (Andersen *et al*, 2002, 2005; Dow-Edwards and Busidan, 2001; Mague *et al*, 2005) (Table 1). It will be interesting to determine if aggressive behavior is analogously affected. Currently, these findings indicate that the sensitive period for the potentiating effect of the stimulant exposure (and possibly the aggression-increasing effect of stimulant exposure) might reside in a narrower window, which is positioned in late rather than early adolescence. Indeed, rats exposed to cocaine from P28 to P34 exhibit sensitized responses to cocaine challenge at P37, P48, and P96 (Brandon *et al*, 2001; Table 1). Likewise, preliminary data from our lab indicate that P32–P41 DAT blockade is sufficient to increase adult aggression and amphetamine response in mice (personal communication MSA; Table 1). These findings demonstrate that altered DAergic signaling can impact adult behavior as a function of developmental timing. Together, these data therefore suggest that permanent changes in aggressive behavior and stimulant sensitivity are jointly defined based on the developmental period during which monoaminergic interference occurs, the monoamine system targeted by the interference, and the valence of the interference.

Mechanistic Insight on the PA Establishment of Perturbed Emotionality

The classic aggression circuitry involves hypothalamic areas and the periaqueductal gray (PAG), with upstream control of these regions being provided by the septum, the amygdala, and PFC (Dalley *et al*, 2011; Davidson *et al*, 2000; Pavlov *et al*, 2012) (Figure 3). Electrical stimulation of the intermediate hypothalamic area and the VMH (the 'hypothalamic attack area') leads to aggressive behavior in cats and rats (Hess, 1928; Kruk *et al*, 1979, 1983; Lammers *et al*, 1988; Roeling *et al*, 1994; Wasman and Flynn, 1962). More recently, pharmacogenetic and optogenetic studies have confirmed these findings in mice, and have refined neuroanatomical, cellular, and conceptual insight. Specifically, optogenetic stimulation of neurons in the ventrolateral subdivision of the VMH (VMHvl) causes male mice to attack males, females, and inanimate objects, whereas pharmacogenetic silencing of the VMHvl reversibly inhibits aggression, demonstrating both necessity and sufficiency of this region in certain aggressive behaviors (Lin *et al*, 2011). Intriguingly, the neuronal population responding to aggressive situations is intermingled and overlapping with neurons, which are active during mating (Lin *et al*, 2011). VMHvl neurons send axons to the dorsolateral PAG, electrical stimulation of which also triggers aggression in cats, suggesting that this hypothalamic-PAG pathway is central to the mediation of aggressive behavior (Siegel and Shaikh, 1997). The VMHvl receives afferents from the PFC, the lateral septum, the bed nucleus of the stria terminalis (BNST), the amygdala, and other hypothalamic regions (Toth *et al*, 2010), all of which modulate aggression. Most strikingly, lesions to the rostral lateral septum cause hyperdefensiveness/hyperirritability, a phenomenon called 'septal rage' (Sodetz and Bunnell, 1970). Conversely, septal stimulation decreases aggression (Potegal *et al*, 1980). The amygdala receives input from the HPC, and many cortical and thalamic areas, and sends afferents to the hypothalamus and PAG (Gregg and Siegel, 2001).The amygdala thereby integrates sensory and emotional information to modulate and adapt behavioral output, which includes aggressive behavior (Gregg and Siegel, 2001). Neural inputs from the PFC to the VMHvl originate largely from the mPFC and the orbital frontal cortex (OFC) (Toth *et al*, 2010). Lesions of these cortical regions caused by trauma, tumors, and neurodegeneration result in emotional disturbances, including disinhibited aggressive behavior. Striking lesion examples include Phineas Gage(Damasio *et al*, 1994; Van Horn *et al*, 2012), and patients who had suffered penetrating head injuries during their service in Vietnam (Grafman *et al*, 1996; Pardini *et al*, 2011). Imaging studies further support a role of the mPFC and OFC in modulating aggressive behavior. For example, patients with borderline personality disorder or antisocial personality disorder display reductions in mPFC and OFC volumes (Hazlett *et al*, 2005; Narayan *et al*, 2007; Raine *et al*, 2000). Frontal activity is inversely correlated with history of violence, and impulsive aggressive behavior (Goyer *et al*, 1994; Lee *et al*, 2008; Raine *et al*, 1998; Volkow *et al*, 1995). These studies support a central role of the mPFC and OFC in serving as a top–down 'brake' on the hypothalamic-PAG aggression pathway.

In summary, studies on humans and animal models have identified critical nodes within a complex circuit controlling aggressive behavior. Intriguingly, it overlaps with circuitry controlling fear, anxiety, and mating behavior at the neuroanatomical and even cellular level (Canteras and Graeff, 2014; Lin *et al*, 2011; Silva *et al*, 2013; Tye *et al*,

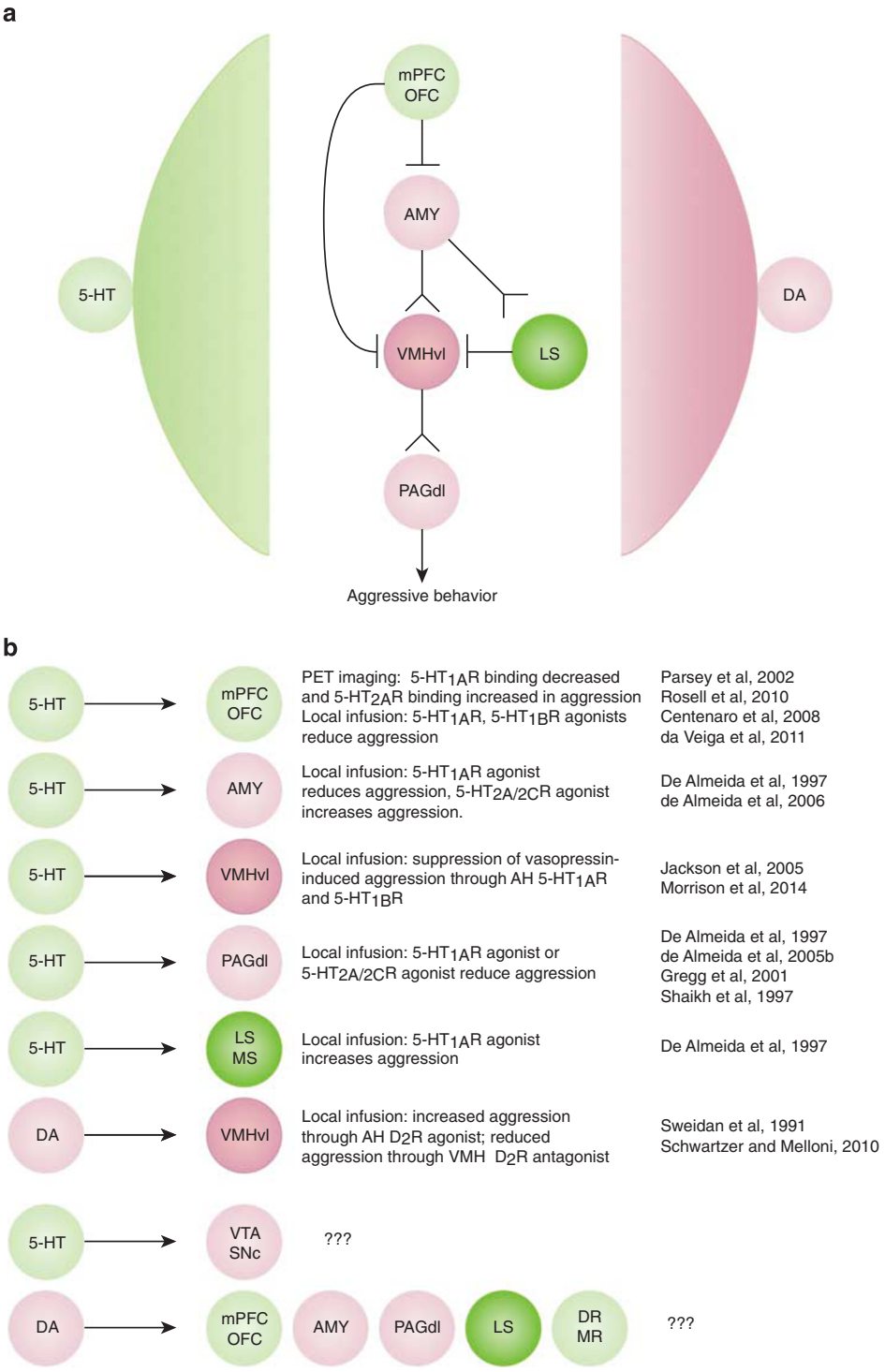


Figure 3. Monoaminergic modulation of aggression circuitry. The central VMHvl–PAG aggression pathway is most prominently controlled by the lateral septum (LS), the amygdala (AMY), and mPFC/OFC (a, central part). This aggression circuit in turn is modulated by 5-HT and DA signaling (a, lateral part). Red indicates aggression promoting circuit elements and green indicates aggression ameliorating circuit elements, as revealed through local lesioning, inhibition, and/or stimulation studies. The dark colors for VMHvl and LS indicate the high severity of behavioral consequences elicited by stimulation of the VMHvl (also known as the 'hypothalamic attack area') and septal lesioning (eliciting 'septal rage'). (b) Summary of studies giving insight into the role of local 5-HT and DA signaling in modulating aggressive behavior. AH, anterior hypothalamic nucleus; DA, dopamine; MS, medial septum; PAGdl, dorsolateral periaqueductal grey; 5-HT, serotonin.

2011), indicating that the interdependence of these behaviors is hardwired.

Monoaminergic afferents target the central nodes of this aggression circuitry, and thereby confer modulatory and regulatory consequences on behavior (Figure 3). However, monoaminergic action in target regions depends on several factors ranging from the neuroanatomical connectivity map at the cellular level and the receptor complement present on

the various cell types, to the intensity and pattern of the monoaminergic signal. A few studies have focused on the role of specific receptors within specific regions. PET imaging studies demonstrate a negative correlation between lifetime aggression and 5-HT_{1A} receptor binding in the anterior cingulate, mPFC and OFC, the amygdala, and the dorsal raphe (Parsey *et al*, 2002). Consistently, local infusion of 5-HT_{1A} and 5-HT_{1B} receptor agonists into the ventral OFC decreases aggressive behavior in rodents (Centenaro *et al*, 2008; da Veiga *et al*, 2011). Local infusion of a 5-HT_{1A} receptor agonist into median raphe nucleus, the corticomedial amygdaloid nucleus, or the dorsal PAG also reduces aggressive behavior, whereas conversely local infusion of a 5-HT_{1A} receptor agonist into the medial septal area increases aggressive behavior (De Almeida and Lucion, 1997). In cats, local infusion of a 5-HT_{1A} receptor agonist into the PAG decreases defensive rage behavior elicited by electrical stimulation of the medial hypothalamus (Gregg and Siegel, 2001; Shaikh *et al*, 1997). Finally, 5-HT_{1A} and 5-HT_{1B} receptors modulate aggression by suppressing vasopressin's proaggressive function in the anterior hypothalamus (AH; Jackson *et al*, 2005; Morrison and Melloni, 2014). Together, these studies demonstrate a broad involvement of 5-HT_1 receptor-type signaling in modulating, mostly inhibiting, aggressive behavior. Local infusion of 5-$HT_{2A/2C}$ receptor agonist into the corticomedial amygdaloid nucleus increases, but infusion into the dorsal PAG reduces aggression in female rats (de Almeida *et al*, 2005b, 2006). Interestingly, orbitofrontal availability of 5-HT_{2A} receptors assessed through PET imaging is higher in personality disorder patients with physical aggression when compared with patients without aggression or healthy controls (Rosell *et al*, 2010). These findings are congruent with the role of 5-HT_1-type receptor signaling, indicating that 5-HT-mediated inhibition of PFC activity (5-HT_{1A} and 5-HT_{1B} receptor agonism and 5-HT_{2A} receptor antagonism) acts to decrease aggressive behavior. However, this conclusion contradicts the model in which the PFC serves as a top–down 'brake' on the hypothalamic-PAG aggression pathway. Reconciling these models will require higher resolution knowledge about prefrontal circuitry, taking into consideration 5-HT receptor localization, 5-HT/DA interaction, and local inhibitory and excitatory networks on one hand, and behavioral dissection along different types of aggression and impulsivity on the other hand.

PET imaging studies also give some insight into the role of DA signaling in human aggression. For example, amphetamine-associated striatal DA release is positively correlated with impulsivity (Buckholtz *et al*, 2010a). However, other studies indicate the opposite relationship, finding a negative correlation between levels of aggression and DA storage capacity in the midbrain and the striatum (Schluter *et al*, 2013). Patients suffering from schizophrenia, who display high levels of aggression, show an upregulation of the D_2 receptor in the striatum (Hirvonen *et al*, 2005), and haloperidol and risperidone are often used successfully to alleviate aggression in such patients (Volavka *et al*, 2004b). In cats, apomorphine or D_2 receptor agonist microinjection into the medial preoptic-AH (mPO-AH) facilitates feline affective defense behavior elicited by electric stimulation of the VMH (Sweidan *et al*, 1991). Conversely, D_2 receptor antagonist infusion into the VMH blocks the proaggressive effect of both electrical stimulation and apomorphine potentiation (Sweidan *et al*, 1991). Likewise, D_2 receptor antagonist infusion into the AH of an aggressive Syrian hamster model dose dependently suppressed aggressive behavior (Schwartzer and Melloni, 2010). In a rat model of aggression, local infusion of haloperidol into the NAc reduces aggressive behavior (Beiderbeck *et al*, 2012). Taken together, these findings provide evidence for D_2 receptor mediated promotion of aggression in the mPO-AH, VMH, and NAc.

How does monoamine signaling during the PA sensitive period affect circuit properties to impose changes on aggressive behavior? Monoaminergic systems themselves remain plastic during adolescence, and thus permanent alterations to their function could underlie altered adult behavior. For example, cocaine treatment during adolescence increases aggressive behavior in male Syrian hamsters (Harrison *et al*, 2000), and also leads to deficits in 5-HT afferent innervations to the AH, lateral septum, medial amygdala, and BNST (DeLeon *et al*, 2002). Because 5-HT signaling inhibits the proaggressive effect of vasopressin infusion into the AH, and because electrically evoked vasopressin release in the AH is increased in hamsters after chronic cocaine exposure from P27 to P56 (Delville *et al*, 1996; Ferris *et al*, 1997; Ferris and Potegal, 1988; Jackson *et al*, 2005; Koolhaas *et al*, 1998), a model was put forward in which chronic PA cocaine exposure reduces 5-HTergic afferents to the AH, disinhibiting vasopressin's proaggressive effects (Jackson *et al*, 2005; Morrison and Melloni, 2014). Such a model is consistent with the 5-HT hypothesis of aggression, in particular with hypo-5-HTergic animal models displaying increased aggressive behavior. Nevertheless, the causal relationships of the model remain to be proven and in the context of sensitive period conceptualization, it will be interesting to see if behavioral, anatomical, and physiological consequences are transient or persistent.

Another example suggesting a monoaminergic mechanism is based on the correlation between aggression and the behavioral response to amphetamine (Yu *et al*, 2014): because of the bidirectional consequences on aggression and amphetamine-induced locomotion seen with P22–P41 5-HTT and DAT blockade, it is tempting to speculate that the primary hit occurs at the DA system. In this model, PA DA and 5-HT signaling bidirectionally affect the DA system to opposingly alter aggressive behavior and behavioral response to amphetamine challenge. Alternatively, DAergic and 5-HTergic PA signaling could act on one common, or multiple independent, downstream circuits that affect aggression. Here, high aggression caused by high PA DA signaling should be rescued by concomitant high PA 5-HT signaling. However, PA MAOA blockade blocks both 5-HT and DA metabolism, yet it increases aggression and

behavioral response to amphetamine (Yu *et al*, 2014), indicating that the DA system is downstream of and dominant over the 5-HT system. Such a model is congruent with the DA hypothesis of aggression, and in particular with the enhanced aggressive behavior observed in hyper-DAergic animal. However again, the causal relationships of this model remain to be proven.

Models of general 5-HT hypofunction or DA hyperfunction cannot explain the specificity of behavioral consequences observed with PA monoaminergic perturbations. For example, PA monoamine interference impacts adult aggressive but not affective behavior, but changes to the affective domain would be expected if a globally altered 5-HT system underlies the behavioral sequelae. Likewise, animals with altered aggression do not display altered baseline locomotor activity, which would be expected if a globally altered DA system mechanistically underlies the behavioral sequelae. Hence, it is likely that PA monoamine interference impacts only certain aspects of monoamine systems, such as anatomically defined sub-projections or specific signaling components. An example for the latter mechanism is provided by the consequences of juvenile methylphenidate exposure. Specifically, P20–P35 methylphenidate administration reduces *DRD3* (but not *DRD1*, *DRD2*, *DRD4*, or *DRD5*) expression in the mPFC (but not NAc or striatum) at P60 in rats (Andersen *et al*, 2008), and these changes are associated with differential molecular responses to DA system targeting drugs (Andersen and Sonntag, 2014).

Lastly, many circuit elements downstream of monoaminergic synapses could carry the critical changes that are responsible for the behavioral phenotypes. For example, the functional connectivity between the central mediators and modulators of aggressive behavior, the septum, the amygdala, the PFC, the VMH, and the PAG, might be permanently established through PA monoamine signaling. The most prominent albeit still somewhat indirect examples in support of this model stem from human imaging studies. Humans carrying the *MAOA-L* allele, which is associated with increased aggression and impulsivity, also demonstrate aberrant coupling between the amygdala and the ventromedial PFC when exposed to emotionally relevant stimuli (Buckholtz and Meyer-Lindenberg, 2008; Dannlowski *et al*, 2009). Furthermore, metabolic activity between right OFC and ventral amygdala is tightly coupled in healthy subjects but not in patients with borderline personality disorder (New *et al*, 2007). In animal models, optogenetic tools can be applied to assess physiological connectivity and to investigate the relationship between circuit parameters such as connectivity and behavior. Therefore, these tools will have an important role in testing alternative models and in elucidating circuitry-related mechanisms.

PA Adversity and Monoamine Perturbation

Adolescence is a vulnerability window for stress exposure to elicit long-lasting behavioral consequences. Human adolescents exhibit greater stress reactivity than non-adolescents (Dahl and Gunnar, 2009) and PA stress can trigger the onset of neuropsychiatric disorders, most prominently schizophrenia and substance abuse (Hoffman and Dobscha, 1989). Furthermore, chronic stress during adolescence impacts PFC development (Casey *et al*, 2010, 2011; Hoftman and Lewis, 2011; Lupien *et al*, 2009; Selemon, 2013) and is associated with lower cognitive performance in adulthood, both in humans (Casey *et al*, 2010; Rahdar and Galvan, 2014) and rodents (Lukkes *et al*, 2009). Interestingly, although the DA system undergoes a transient expansion phase of high plasticity during adolescence (Figure 1), stress exposure can influence its maturation. Exposure to social defeat stress during adolescence, and not adulthood, for example reduces basal extracellular levels of DA in the mPFC but not NAc (Watt *et al*, 2009) and increases behavioral response to amphetamine challenge (Burke *et al*, 2013). mPFC DA release inhibits glutamatergic input to the NAc (Thierry *et al*, 1986), hence disinhibition of this pathway might underlie the locomotor enhancing effect. Similarly, post-weaning stress through isolation rearing decreases DA turnover in mPFC (Heidbreder *et al*, 2000), but enduringly increases both basal and stimulant-induced DA levels in NAc (Hall *et al*, 1998; Jones *et al*, 1992). Together, these data indicate enhanced mesolimbic and reduced mesocortical DAergic activity as a consequence of PA stress.

Although 5-HT system maturation precedes DA system maturation (Lambe *et al*, 2000), PA stress still impacts the 5-HT system. Isolation rearing decreases basal 5-HT turnover in the NAc (Heidbreder *et al*, 2000), but not in the PFC or caudate putamen (Jones *et al*, 1992). However, isolation rearing increases NAc 5-HT release in response to inescapable foot shock and associated context exposure (Fulford and Marsden, 1998, 2007). Conversely, isolation stress attenuates amphetamine-, KCl- and novelty-evoked 5-HT release in the PFC and HPC (Bickerdike *et al*, 1993; Dalley *et al*, 2002), whereas post-weaning social isolation and maternal separation, change 5-HT fiber density in hypothalamic areas involved in aggression (Haller, 2013).

Together, these findings demonstrate reorganization of the DAergic and 5-HTergic systems in response to PA adversity, which might impact adult behaviors including aggression.

Clinical Relevance

Aggressive behavior has a large societal impact and contributes to the pathology of a number of psychiatric conditions including psychotic disorders, anxiety disorders, attention deficit disorder, drug abuse, and suicide. Elucidating the developmental contribution to pathological aggression is central to understanding its pathophysiology, and thus critical to advance our understanding of these disorders in order to ultimately devise effective prevention and treatment strategies. Human aggressive behavior has its roots in infant development, but during childhood and adolescence control of aggressive impulses is established

(Cote *et al*, 2007; Nagin and Tremblay, 1999; Tremblay and Szyf, 2010). Thus, there are two conceptual developmental phases for the establishment of adult aggressive behavior, (1) the establishment of baseline aggression and (2) the establishment of the control of baseline aggression. Both phases are influenced by genetic and environmental factors (Cote *et al*, 2007). Highlighted in this review is the latter phase, which passes through a 5-HT- and DA-sensitive period, and to the best of our knowledge impacts circuit maturation of systems such as the monoaminergic systems and the PFC, which ultimately control and modulate the central hypothalamic-PAG pathway. Findings on the 5-HT- and DA-sensitive PA period comport with human vulnerabilities to aggression conferred by functional genetic polymorphisms. For example, aggressive behavior has been associated with loss-of-function and low-expressing *MAOA* alleles (Brunner *et al*, 1993; Buckholtz and Meyer-Lindenberg, 2008; Caspi *et al*, 2002; Zalsman *et al*, 2005), the *10R* variant of *DAT1* (Bedard *et al*, 2010; Guo *et al*, 2007), and the low-activity met allele of the *COMT* (Volavka *et al*, 2004a). The sensitive period model predicts that these risk alleles act primarily during PA to alter brain maturation and circuit formation leading to altered behaviors.

A specific type of environmental factor relevant to the 5-HT- and DA-sensitive PA period is drug exposure. Because molecules targeting monoamine signaling constitute the most widely prescribed (eg, antidepressants/anxiolytics) and/or abused (eg, amphetamine, methamphetamine, cocaine) psychoactive drugs in the markets today, their use during adolescence might significantly impact public health, beyond their prescribed or recreational purpose. For example, SSRIs taken during PA might impact brain maturation to reduce adult aggression, whereas stimulant exposure during PA could increase adult aggressive behavior. More data is needed to understand human relevance and adequately compare risks and benefits, especially of prescribed medication, but some findings already indicate translatability. For example, chronic stimulant exposure increases aggressive behavior in rodents, non-human primates and humans (Dawe *et al*, 2009; Martin *et al*, 1990; Sokolov *et al*, 2004), even in abstinent stimulant users (Sekine *et al*, 2006). Furthermore, human individuals with antisocial traits also show mesolimbic DA hypersensitivity to amphetamine, as impulsivity is positively correlated with the magnitude of amphetamine-induced DA release in the striatum (Buckholtz *et al*, 2010a).

On the basis of the notion that DAergic abnormalities contribute to specific complex disorders such as schizophrenia and substance abuse, the PA 5-HT- and DA-sensitive period might have broader etiological relevance for psychopathologies beyond aggression. In this context, it is important to emphasize the bidirectional characteristic of the monoaminergic modulation of brain development and adult behavior. Thus, findings not only give insight into risk factors for psychopathology (exposure as a function of time, disrupting brain development to negatively impact adult function), but also reveal potential preventive treatment approaches (exposure as a function of time, normalizing brain development to positively impact adult function).

OUTLOOK

The available data demonstrate the existence of sensitive periods that influence life-long vulnerability to anxiety, depression, aggression, and substance abuse. Such sensitive periods have been most extensively characterized for sensory systems (eg, visual cortex), but conceptually similar principles apply to the development and organization of brain circuitry that mediate the more complex behaviors described here. Specifically, we have reviewed three sensitive periods during which transiently altered monoamine signaling carries long-lasting consequences on adult brain function.

Respective findings lead to the following three working hypotheses:

1. Any manipulation, which increases 5-HT signaling during development (P0–P4 in mice), will impair somatosensory cortex maturation and lateral geniculate nucleus/superior colliculus topography.
2. Any manipulation, which increases 5-HT signaling during development (P2–P11 in mice), will increase adult anxiety/depression-like behavior and impair cognition.
3. Any manipulation, which increases DA signaling during development (P22–P41 in mice), will increase adult aggression and behavioral response to stimulants, whereas any manipulation that increases 5-HT signaling during that same period will decrease adult aggression and behavioral stimulant sensitivity.

Respective findings have the following three translational implications:

1. Genetic and environmental factors, which affect 5-HT signaling during gestational development, act in concert to predispose to, or protect against, impaired topography within somatosensory and visual system neurocircuitry.
2. Genetic and environmental factors, which affect 5-HT signaling during late gestational development, act in concert to predispose to, or protect against, depression and anxiety disorders and cognitive dysfunction.
3. Genetic and environmental factors, which affect DA and 5-HT signaling during adolescence, act in concert to predispose to, or protect against, high aggression and DA dysfunction.

Relevance is underscored by the multitude of known rare and common functional variants in genes impacting 5-HT and DA signaling, the impact of the omnipresent environmental factor ‘stress’ on monoamine signaling, and the high frequency in the use of drugs and medications that target the 5-HT and DA systems.

Furthering our knowledge of sensitive periods that determine the developmental trajectory of complex

behaviors is a necessary step toward improving prevention and treatment approaches for neuropsychiatric disorders. Preclinical studies will continue to identify neurobiological correlates of disordered behaviors and test causal relationships in current and future neuropathology models, leading the way to novel treatment approaches. Genetic studies might take advantage of the predicted converging effects of multiple genetic factors on monoaminergic signaling. Likewise, gene × environment or environment × environment interaction studies might analyze the impact of various factors that converge on specific monoamine signaling pathways. Longitudinal and population-based epidemiological studies investigating the side effects of drugs and medications years after cessation of consumption/treatment are essential.

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