Published in final edited form as:
J Autism Dev Disord. 2009 February ; 39(2): 260–268. doi:10.1007/s10803-008-0624-0.

Pleiotropic Effects of Neurotransmission during Development: Modulators of Modularity

Barbara L. Thompson and
Department of Pharmacology; 8114 MRBIII, Nashville, TN 37232, USA; (615) 936-3865 (phone); (615) 936-3747 (fax); barbara.thompson@vanderbilt.edu

Gregg D. Stanwood
Department of Pharmacology, Vanderbilt Kennedy Center for Research on Human Development, & Center for Molecular Neuroscience; 8405 MRBIV, Nashville, TN 37232, USA; (615) 936-3861 (phone); (615) 936-2202 (fax); gregg.stanwood@vanderbilt.edu

Abstract

The formation and function of the mammalian cerebral cortex relies on the complex interplay of a variety of genetic and environmental factors through protracted periods of gestational and postnatal development. Biogenic amine systems are important neuromodulators, both in the adult nervous system, and during critical epochs of brain development. Abnormalities in developmental programming likely contribute to developmental delays and multiple neurological and psychiatric disorders, often with symptom onset much later than the actual induction of pathology. We review several genetic and pharmacological models of dopamine and serotonin modulation during development, each of which produces permanent changes in cerebral cortical structure and function. These models clearly illustrate the ability of these neurotransmitters to function beyond their classic roles and show their involvement in the development and modulation of fine brain circuitry that is sensitive to numerous effectors. Furthermore, these studies demonstrate the need to consider not only gene by environment interactions, but also gene by environment by developmental time interactions.

Keywords

dopamine; serotonin; cortex; cocaine; prenatal; postnatal

Introduction

Defects in the development of the cerebral cortex can have a profound impact on mature brain functions. Developmental anomalies in cortical development contribute to neuropsychiatric disorders such as schizophrenia (Lewis & Levitt, 2002; Weinberger, 1995), mental retardation, learning disabilities and autism (Charman, 1999; Levitt et al., 2004). The molecular and cellular bases that tie developmental defects to cortical dysfunction in these disorders remain unknown, but influences on cell-cell interactions that mediate specific developmental events are likely targets. This also seems to be true for non-genetic insults, such as prenatal exposure to toxicants, stress or drugs of abuse (Andersen, 2005; Rodier, 1995; Stanwood & Levitt, 2004; Trask & Kosofsky, 2000).

The biogenic amine neurotransmitters dopamine (DA), serotonin (5-HT) and norepinephrine (NE) are pleiotropic molecules (that is, each can produce multiple, diverse effects) that serve as regulators of distinct cellular functions at different times in neurodevelopment and adulthood. In this review, we will describe several key animal models which have examined the structural and functional consequences of altering these neurotransmitters in development.

We hypothesize that genetic and environmental modulation of biogenic amines, during discrete sensitive periods of brain development (Knudsen, 2004; Rodier, 1994; Stanwood & Levitt, 2004), alter the formation and function of brain circuitry and modulate the development of modularity within the cerebral cortex.

Example 1: 5-HT and the Development of Anxiety Circuits and Behavior

5-HT is a well known modulator of behavioral, physiological and emotional functions, including learning and memory, appetite, temperature regulation, and mood (Albert & Lemonde, 2004; Hedlund & Sutcliffe, 2004; Holmes *et al.*, 2005; Lucki, 1998; Meneses, 1999; D. L. Murphy & Lesch, 2008; Ressler & Nemeroff, 2000; Silverstone, 1992). Dysfunctions of serotonergic signaling may contribute to disorders including anxiety, aggression, depression, and autism (Burgess *et al.*, 2006; Canli & Lesch, 2007; Leonardo & Hen, 2006; Mann *et al.*, 2001; Popova, 2006; Sutcliffe *et al.*, 2005). In the mammalian nervous system, 5-HT exerts its effects by binding to at least 15 distinct receptor subtypes, each with unique pharmacological properties, distribution, and activational profiles. The high affinity 5-HT transporter, by transporting 5-HT back into the presynaptic terminal, is the primary means of 5-HT removal from the synapse and extracellular fluid.

Developmentally, 5-HT signaling modulates cellular functioning even before the onset of neurogenesis, including events in the periphery such as craniofacial, gastrointestinal, and cardiovascular morphogenesis (Buznikov *et al.*, 1996; Lauder, 1983; Whitaker-Azmitia, 1991; Whitaker-Azmitia *et al.*, 1996). Maternal 5-HT has also been observed to influence left-right patterning in frog and chick embryos (Fukumoto *et al.*, 2005); additional evidence also implicates maternal serotonin in mouse embryogenesis (Cote *et al.*, 2007). Within the brain, 5-HT and its receptors are expressed early in prenatal development (Bonnin *et al.*, 2006; Bonnin *et al.*, 2007; Goldman-Rakic *et al.*, 1990; Lambe *et al.*, 2000; Whitaker-Azmitia *et al.*, 1987), and can modify elements of dendritic and axonal differentiation (Bonnin et al., 2007; Persico et al., 2006) (see also Example 2, below). The discovery of alterations in thalamocortical development and somatosensory cortex cytoarchitecture in monoamine oxidase A knockout mice (this is the enzyme largely responsible for serotonin degradation in rodents) led to a recognition that different components of aminergic signaling might specifically influence discrete ontogenic events (Cases et al., 1996; Luo et al., 2003).

Genetic elimination of 5-HT_{1A} receptors and the 5-HT transporter, along with known 5-HT pharmacology, implicated the 5-HT system in anxiety and depression (Holmes et al., 2003; Parks et al., 1998; Ramboz et al., 1998). To test for a possible developmental role of the 5-HT_{1A} receptor in establishing anxiety circuitry, Hen and colleagues generated a conditional knockout mouse that allowed for temporally-restricted rescue of postsynaptic 5-HT_{1A} receptors in the cerebral cortex and hippocampus (Gross et al., 2002). Using this strategy, they demonstrated that initiating expression of the receptor after postnatal day (P) 21 resulted in increased anxiety levels identical to constitutive 5-HT_{1A} receptor knockout animals. Conversely, earlier expression of the 5-HT_{1A} receptor, during the first three postnatal weeks, produced mice with anxiety levels that were indistinguishable from wild-type animals, even if the receptor was turned off in adulthood. These findings indicate that 5-HT_{1A} receptors are essential to the establishment of normal anxiety-modulating circuits in the brain during early postnatal development in the rodent. In humans, this time frame would include the third trimester of pregnancy, and infancy (Clancy *et al.*, 2007; Dobbing & Sands, 1979; Rodier, 1980).

Constitutive knockout of the 5-HT transporter also leads to increases in anxiety and alterations in cortical and subcortical information processing. This led to an intriguing study in which mice were administered the selective serotonin reuptake inhibitor (SSRI) fluoxetine from P4-

P21, producing a pharmacological equivalent of a temporally restricted knockout (Ansorge et al., 2004). This treatment induced effects on anxiety behaviors that are quite similar to the 5-HT transporter gene knockout. Another group examined the effect of administration of the SSRI citalopram during P8–21 in rats, and observed long lasting effects on 5-HT metabolism and behavior (Maciag et al., 2006). Taken together, the 5-HT_{1A} rescue experiments and early postnatal SSRI models suggest that 5-HT plays a critical role in the maturation of circuits relevant to anxiety prior to the third postnatal week. Intriguingly, a recent study examined the effects of foot-shock stress during P7–13 on adult responses and found no effects on anxiety in either wildtype or 5-HT transporter knockout mice (Carroll et al., 2007). These data suggest that the key sensitive period for altering adult anxiety responses may be between P14 and P21 in the rodent (Figure 1).

Different circuits and brain regions may have different sensitive ontogenic periods. Prenatal exposure to fluoxetine in rats (embryonic days (E)6-E20) was found not to significantly alter anxiety behavior in adult offspring (Bairy et al., 2007). Furthermore, recent work has implicated the activity of the 5-HT synthesis enzyme tryptophan hydroxylase in the proper maturation of sensorimotor gating between P21-P24 (Nakamura et al., 2006).

Consistent with the rodent models, data from human studies suggest that baseline anxiety levels are influenced early in life. By 2 years of age, most children have established cohesive patterns of response to novel environments, as measured by behavioral inhibition. These measures appear to be stable over many years (Hirshfeld et al., 1992; Rosenbaum et al., 1993; Schwartz et al., 1999) (although see also (Degnan & Fox, 2007)), and can predict one's future risk of anxiety disorders (Kagan & Snidman, 1999; Kagan *et al.*, 2007).

Not surprisingly, polymorphisms in 5-HT receptors, signaling partners, synthesis enzymes, and the 5-HT transporter have all been associated with anxiety- and depression-related symptoms and even autism (Albert & Lemonde, 2004; Dannlowski *et al.*, 2008; Kim *et al.*, 2006; D. L. Murphy & Lesch, 2008; Sutcliffe et al., 2005; Walderhaug *et al.*, 2007). Moreover, many prominent psycho-therapeutics target the 5-HT system and are utilized for depression and anxiety among pregnant and nursing mothers. When behavioral therapy is not effective in treating depression in a pregnant woman, the potential risk of drug therapy must be weighed against the considerable risk for relapse of the disorder if pharmacological therapy is interrupted. Published literature to date suggests only modest alterations in neonatal outcome (Andrade et al., 2008; Maschi et al., 2008; Oberlander et al., 2008; Pearson et al., 2007), but given the likelihood of 5-HT modulation of brain circuitry raised by the animal data reviewed above, further study of the neurobehavioral consequences of antidepressant exposure on the developing fetus and infant are clearly warranted. Further, environmental toxicants such as organophosphate insecticides clearly alter developing serotonin systems with permanent consequences (Slotkin & Seidler, 2005); limiting exposures to such environmental chemicals and identifying strategies to ameliorate these effects are crucial.

Example 2: 5-$HT_{1B/1D}$ Receptor Activation Influences Thalamocortical Development

The next example illustrates the ability of the biogenic amines to directly influence cortical modularity. Specifically, we review data demonstrating cortical modulation is based on the effects of 5-HT signaling on the responsiveness of thalamocortical axons to guidance cues. In a detailed neuroanatomical study, Bonnin et al (Bonnin et al., 2006) demonstrated that expression patterns of select serotonin receptors overlapped with those of axon guidance receptors, including netrin receptors, in the embryonic mouse thalamus. In a follow-up study, the authors performed a series of *in vitro* explants studies to examine the response of thalamic axons to different guidance cues, and the role of serotonin in this response (Bonnin et al.,

2007). It was found that the normal attraction of axons from posterior thalamic explants to netrin was reversed when the explants were simultaneously exposed to serotonin. Further experiments determined that this switch was due to activation of the 5-$HT_{1B/1D}$ receptors, as 5-$HT_{1B/1D}$ antagonists blocked the switching capacity of serotonin, and 5-$HT_{1B/1D}$ agonists directly mimicked the actions of serotonin. Elegant *in utero* electroporation studies then revealed that directly over-expressing or reducing 5-$HT_{1B/1D}$ receptor expression *in vivo* altered thalamocortical axon trajectory and distribution, demonstrating a direct neuromodulatory role for 5-HT in the developing mouse brain (Bonnin et al., 2007).

These experiments further illustrate the importance of normal 5-HT signaling during development. Altering 5-HT expression can disrupt normal development of brain circuitry, thereby increasing the risk of neurodevelopmental disorders.

Example 3: Overexpression of Subcortical Dopamine D_2 Receptors Alters Dopaminergic Responsiveness in the Prefrontal Cortex

Our next two examples are drawn from dopamine, and its effects on cortical modularity. An intriguing model system recently created within the dopaminergic system involves conditional transgenic mice over-expressing dopamine D_2 receptors in the striatum (Kellendonk et al., 2006). Striata of the transgenic mice contain increased numbers of D_2 receptor binding sites and increased effects on adenylyl cyclase, indicating that the transgenic receptors are functional. Adult mutant mice exhibit normal locomotor activity, sensorimotor gating, and anxiety behaviors. However, the mice display substantial defects in working memory tasks and behavioral flexibility typically associated with prefrontal cortical dysfunction. Consistent with this, the mutant mice display altered glucose metabolism, dopamine levels, and dopamine D_1 receptor activation in the prefrontal cortex. An advantage of this mouse model is that over-expression of the transgenic receptor can be regulated temporally, such that administration of doxycycline restores dopamine D_2 receptor to normal levels. Interestingly, doxycycline treatment in the adult does not reverse the cognitive defects, indicating that these deficits reflect striatal D_2 receptor over-activity during fetal life. A recent follow-up study suggests that the effects of exogenous D_2 receptor over-expression on interval timing in an operant task also are established developmentally, whereas motivational processes can be normalized by transgene elimination in the adult (Drew et al., 2007). Direct assessment of cortical architecture and connectivity in this model is still needed.

Example 4: Developmental Loss of Dopamine D_1 Receptor Signaling Induces Alterations in Cortical Architecture and Function

This next example again demonstrates how monoamines can directly modify cortical development. Administration of cocaine *in utero* alters dopamine neurotransmission. The extent to which this prenatal exposure affects the development of the human fetus varies significantly, but it has been consistently established that there are long-term consequences, ranging from relatively mild to severe functional disruptions in cognition and attention (Dow-Edwards *et al.*, 1999; Gingras & O'Donnell, 1998; Karmel & Gardner, 1996; Mayes *et al.*, 1998; Richardson *et al.*, 1996; Singer *et al.*, 2004).

Different animal models, designed to mimic human drug use during gestation, confirm that prenatal cocaine exposure results in specific behavioral, cellular, and molecular changes that appear to be permanent (Harvey, 2004; Lidow, 2003; Mayes, 2002; Stanwood & Levitt, 2004). Our lab has developed a unique animal model of prenatal cocaine exposure to study the mechanisms underlying the complex, long-term adaptive changes and the functional outcomes of *in utero* cocaine exposure. This model utilizes a low-dose regimen of intravenous prenatal cocaine exposure in the rabbit, which was initially selected for ease of intravenous

administration. Furthermore, the pharmacokinetic profile of intravenous cocaine in the rabbit (Parlaman et al., 2007) closely models what is seen when human users abuse cocaine (Evans et al., 1996; Jenkins et al., 2002), allowing for direct species comparisons and interpretations. A number of studies have established that the prenatal dosing is not teratologic, nor does it impact basic developmental parameters such as kit mortality, litter size, sex or growth rates (L. Jones *et al.*, 1996; E. H. Murphy *et al.*, 1997; X. H. Wang *et al.*, 1995b; X. H. Wang *et al.*, 1996). However, through control of length of drug exposure, age at drug exposure, and dosing, we have delineated a critical window of time (E 16–25, Figure 1) during which exposure to cocaine affects behavior, morphology, and cellular composition (Stanwood & Levitt, 2003; Stanwood *et al.*, 2001a; Stanwood *et al.*, 2001b; B. L. Thompson *et al.*, 2005b). This window of time corresponds to the emergence of pre- and postsynaptic components of the DA system in the cerebral cortex (Stanwood et al., 2001a).

Our neuroanatomical and molecular analyses following prenatal cocaine exposure have delineated a number of highly specific changes in DA-rich cortical areas, including changes in GABA content, calcium binding protein expression, and a 40–50 percent increase in pyramidal neuron apical dendrite length within DA rich cortical areas (L. B. Jones *et al.*, 2000; E. H. Murphy et al., 1997; Stanwood & Levitt, 2001; Stanwood & Levitt, 2007; Stanwood *et al.*, 2006; Stanwood et al., 2001b). These cortical areas are involved in cognition and executive functioning tasks, including attention (Clark *et al.*, 2004; Collette & Van der Linden, 2002; Elliott, 2003; Elston, 2003; Goldman-Rakic, 1996).

Consistent with the regional selectivity in the anatomical findings, extensive behavioral characterization of rabbits following *in utero* exposure to cocaine suggest that the behaviors disrupted appear to be limited to those mediated via select DA-rich cortical and sub-cortical regions (Stanwood & Levitt, 2003; B. L. Thompson et al., 2005b). For example, these animals exhibit decreases in spontaneous alternation as measured by the Y-maze following prenatal cocaine exposure. This decrease in attention is not accompanied by changes in open field behavior or two-object recognition. Additionally, offspring exposed to prenatal cocaine show a decreased number of head-bobs, a measure of stereotypy, following a single injection of amphetamine and display a blunted preference for cocaine in a conditioned place preference paradigm (Stanwood & Levitt, 2003; B. Thompson *et al.*, 2005a).

Molecular analyses have determined that the dopamine D_1 receptor exhibits permanent reduced coupling to its cognate G-protein, $G_{s\alpha}$, following prenatal cocaine exposure (Friedman *et al.*, 1996; L. B. Jones et al., 2000; H. Y. Wang *et al.*, 1995a). This reduction in coupling is a result of dopamine D_1 receptor remaining internalized and not trafficking properly to the cell membrane where it would then interact with $G_{s\alpha}$ (Stanwood & Levitt, 2007). Adult rabbits exposed to cocaine prenatally also exhibit greatly reduced psychostimulant-induced stereotypies, consistent with diminished D_1 receptor signaling (Simansky & Kachelries, 1996; Stanwood & Levitt, 2003). Additional evidence to support a role for altered D_1 receptor signaling in the cellular findings comes from our recent study of the D_1 receptor knockout mouse, which exhibits similar cellular and morphological changes to the prenatal cocaine exposed rabbits (Stanwood et al., 2005). In contrast, D_1 receptor overexpression has the opposite effects on dendritic architecture (Song *et al.*, 2002).

There are two very important points to emphasize with respect to these findings. First, there is temporal requirement for all of the above results. Specifically, cocaine must be given while the dopaminergic system is simultaneously developing in the embryo. If cocaine is given before the DA system begins to develop, the neuroanatomical and behavioral changes are not observed. Second, there is spatial specificity to these data. The biochemical, morphological, and cellular alterations are only found within DA rich cortical and sub-cortical areas. Non-DA rich areas do not display similar disruptions following prenatal cocaine exposure.

Example 5: Developmental Exposure to a β Adrenergic Receptor Agonist Disrupts Cortical Development

Terbutaline is a β2-adrenergic receptor agonist that is wide used to abate preterm labor because of its ability to cause uterine muscle relaxation. Terbutaline crosses the placental and blood-brain barriers, suggesting that it might also activate fetal β adrenergic receptors on developing neurons and glia. In fact, alterations in glucose metabolism and tachycardia have been observed in neonatal offspring of women treated with terbutaline. Moreover, children exposed to terbutaline or related drugs prior to birth appear to show impaired school performance, cognitive dysfunction, and increased incidence of neuropsychiatric disease (Feenstra, 1992; Hadders-Algra *et al.*, 1986; Pitzer *et al.*, 2001). Although still preliminary, recent data suggest that functional polymorphisms in the β2 receptor may be associated with autism (Cheslack-Postava *et al.*, 2007; Connors *et al.*, 2005).

Neurochemical and neuroanatomical findings in animal models suggest that during particular times of gestation terbutaline can enter the fetal brain and alter patterns of cellular differentiation and synaptogenesis, perhaps via increases in cAMP (Slotkin *et al.*, 2003). In particular, loss of cerebellar Purkinje cells, cerebellar thinning, a reduction in the proportion of pyramidal neurons in the somatosensory cortex with a concomitant increase in smaller nonpyramidal cells, and sex-dependent neuroglial activation have all been reported (Rhodes *et al.*, 2004; Zerrate *et al.*, 2007). In the rat, early postnatal development (P2-P5) appears to be a very vulnerable period (see Figure 1), corresponding to early third trimester in human (Rhodes et al., 2004), when the drug is utilized clinically. Providing an intriguing example of how multiple environmental exposures can influence one another, neonatal terbutaline exposure (P2–5) augments the long-lasting and deleterious effects of later exposure to the insecticide chlorpyrifos (P11–14) (Meyer *et al.*, 2005).

Summary

In recent years, diverse roles for classical neurotransmitters, in particular DA, NE and 5-HT, have been described in the developing brain. Disruption of these signaling pathways during development can lead to permanent alterations in neuronal signaling, brain architecture and behavioral outcome, depending on the time at which disruption occurs. Thus, altering DA, NE or 5-HT neurotransmission during discrete prenatal and early postnatal periods disrupts the developmental processes that establish essential functional circuits required for typical adult function.

Insights into the developmental role of these neurotransmitters primarily have come from animal models. These animal models provide the opportunity to manipulate directly key developmental variables and measure their functional outcome. Through such manipulations, the scientific community is beginning to identify gene by environment interactions that alter developmental trajectory, bringing us closer to understanding the etiology of developmental disorders. However, as the studies highlighted in this paper illustrate, there can be different outcomes based on the developmental state during which the genetic or environmental insult occurs. The delineation of additional “sensitive” and “critical” periods of neurodevelopment is a crucial next step in understanding both normal biology and pathophysiology. As the incidence of neurodevelopmental disorders rises, we emphasize that the relevant variable of developmental time must be included when considering the role of gene by environment interactions in the etiology of neuropsychiatric and neurological disease.

Acknowledgments

Drs. Thompson and Stanwood currently receive support from NICHD core grant P30HD15052 (GDS), F32DA020981 (BLT) and the Vanderbilt Kennedy Center (GDS & BLT). We thank Dr. Pat Levitt for useful discussions, insightful comments, and partial financial support. We also thank Dr. Kathie Eagleson and Dr. Daniel Campbell for critical reading of this manuscript.

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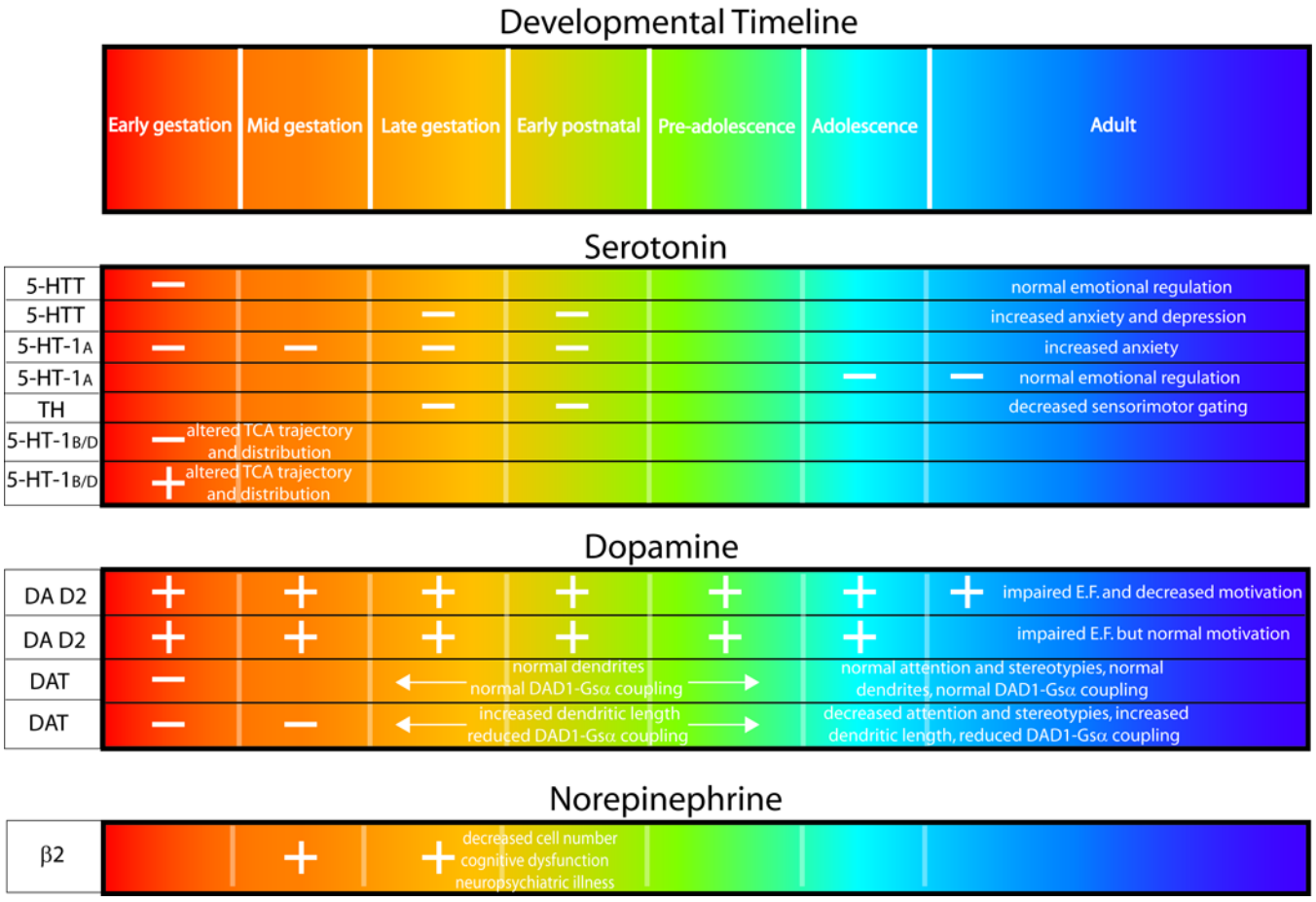

Figure 1.