Antidepressants and adolescent brain development

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Despite being a first-line treatment for adolescent depression and anxiety, antidepressant drugs appear to have questionable efficacy and carry an increased risk of adverse effects in this population. The neural mechanisms underlying this phenomenon are currently unknown. Recent research into the neural effects of alcohol and recreational drugs suggests that the developmental trajectory of the adolescent brain may be particularly vulnerable to pharmacological disturbance. It is therefore important to consider whether prescription psychotropic drugs may have analogous effects. This article reviews the contribution of recent preclinical, clinical and pharmacogenetic literature to current knowledge on the short-term and enduring neural effects of antidepressants on the adolescent brain, with a particular focus on the major neurotransmitter systems and neuroplasticity.

Review
Future Neurology

The idea that the developing brain is a highly malleable structure that is particularly vulnerable to environmental toxins has long been recognized. Both the preclinical and human literature has repeatedly demonstrated that prenatal and early life exposure to a variety of drugs can have untoward and lasting consequences on brain development (see [1–3] for reviews). Examples include methamphetamine-induced disturbances in dopaminergic regions [4] and the widespread structural and functional abnormalities apparent in individuals with fetal alcohol spectrum disorders [5]. The last decade has brought increasing recognition that this period of vulnerability is not limited to early life. Instead, the brain continues to undergo extensive reorganization and growth during childhood and adolescence and into early adulthood, rendering it susceptible to environmental influences throughout these periods. While much of the literature has focused on the characteristics of the adolescent brain in terms of vulnerability to addiction and susceptibility to the toxicity of alcohol, nicotine and illicit drugs [6–12], there is increasing recognition that the susceptibility of this period also extends to the effects of psychotropic drugs, including antidepressants, stimulants and antipsychotics [13–15]. Children and adolescents are not little adults, and often display different behavioral and neural responses to pharmacological manipulations.

However, there is debate on whether the malleability of the brain during adolescence is a window of opportunity in which treatment might allow greater potential for adaptive recovery or whether exposure to psychotropic medications may have enduring negative effects [14]. Given the recent increases in the prescription of psychotropic drugs to children and adolescents [16] and the explosion in the diagnosis of psychiatric disorders in this population [17,18], a detailed knowledge of the immediate and long-term effects of such drug treatment is vital to informing clinical practice. In this article, we review and discuss the current knowledge on both the immediate and long-term neural effects of antidepressant treatment during late childhood and early adolescence.

Adolescent neural development

Adolescence is broadly defined in terms of the transition from childhood to adulthood, or dependence to independence, occurring approximately between the ages of 12 and 20 years in humans [6]. Other species have a corresponding developmental stage marked by similar behavioral and neural changes [12]. In male rodents, for example, adolescence occurs from around postnatal day (P)28 until P55, with sexual maturity occurring at approximately P45 [12,19]. As in female humans, this life stage begins and ends slightly earlier in female rodents, spanning from approximately P25 until P42 [12].

Much of our knowledge of brain development in late childhood and adolescence comes from cross-sectional studies using rodents or from post-mortem human data [20]. More recently, however, the development of MRI technology has afforded the ability to noninvasively gather longitudinal data on overall structural and tissue-specific developmental trajectories [21]. Several comprehensive and recent reviews summarize these findings in detail (e.g., [6,13,20,22]); therefore, only the most salient features of adolescent brain development will be reviewed here.

Keywords
■ adolescent ■ antidepressant ■ brain development ■ dopamine ■ neurogenesis ■ neuroplasticity ■ norepinephrine ■ pharmacogenetics ■ serotonin ■ SSRI

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Gross structural changes & remodeling

Adolescent brain development can be reduced in its simplest form to five general processes: a 'deeper-to-higher' trajectory; a 'back-to-front' developmental trajectory; early overproduction of synapses followed by pruning; increased myelination and efficiency of signal transduction; and increased connectivity between and within regions. The first of these points refers to the fact that the adolescent brain does not develop in a uniform fashion. Rather, in keeping with the stereotypical adolescent behavioral characteristics of risk taking, novelty and sensation seeking, affective reactivity and increased social interaction [23], maturation of 'deeper' subcortical brain regions precedes that of 'higher' cortical regions involved in cognitive control and decision making [24]. MRI studies demonstrate an inverted U-shaped developmental trajectory in gray matter volume, with maximal volume reached sometime in late childhood or early adolescence, depending on the lobe [21]. This growth and cortical thinning that follows proceeds in a 'back-to-front' fashion across the cortex: motor and sensory cortical regions mature first, followed by association regions, with higher cortical areas such as the prefrontal cortex (PFC) maturing later [20,21,25]. Cortical thinning and gray matter volume reduction encompasses, but is not limited to, processes of synaptic regression and pruning, particularly of excitatory glutamatergic cortical inputs [12]. Also contributing to the reduction in gray matter is a concurrent increase in myelination [26]. Volumetric increases in white matter occur fairly uniformly across the cortex and are accompanied by increases in anisotropy, facilitating efficient neuronal communication, particularly between subcortical and cortical regions [7,27]. Indeed, an important part of brain maturation is a remodeling and strengthening of connections between limbic regions and the PFC [12], reflected in the marked increase in dopaminergic, serotonergic and cholinergic inputs to the PFC during adolescence [6]. Accordingly, synaptic plasticity [28], neurogenesis [29] and dendritic spine proliferation [30] are elevated in the adolescent brain.

Monoaminergic maturation

Changes at the level of individual neurotransmitter systems are of great relevance in considering the effects of psychotropic drugs on the adolescent brain, many of which work primarily through monoaminergic systems. Modern antidepressants typically inhibit the reuptake capabilities of the serotonin transporter (5-HTT; e.g., the selective serotonin-reuptake inhibitors [SSRIs]) and/or norepinephrine transporter (e.g., serotonin–norepinephrine-reuptake inhibitors [SNRIs] and the tricyclic antidepressants [TCAs]), while the majority of antipsychotics are antagonists of the dopamine and/or serotonin system [31]. Stimulants such as atomoxetine and methylphenidate have both dopaminergic and noradrenergic effects [32].

The extensive functional connectivity between the monoamine systems means that alterations in one system can have consequences on the other systems, with potential developmental implications. For example, the inhibitory effects of serotonin (5-hydroxytryptamine [5-HT]) on dopaminergic outgrowth to the rodent medial PFC during late postnatal development has potential implications for the use of serotonergic drugs during this developmental period [33]. Similarly, 5-HT neurons in the raphe nucleus exert largely inhibitory effects on dopaminergic transmission in the substantia nigra and ventral tegmental area (VTA), key regions of the mesolimbic 'reward' pathway [34]. Thus, the SSRIs, despite their relative selectivity for the 5-HT system, have been shown to indirectly increase dopaminergic activity in these brain regions in adult rats [35]. Conversely, the SSRI escitalopram has inhibitory effects on the firing of noradrenergic neurons in the locus coeruleus (LC) through serotonergic mechanisms [36].

Age-related changes to the monoamine systems vary considerably depending on the sex of the individual, brain region of interest and receptor subtype [6,22]. For example, in the striatum, an important area of the mesolimbic pathway, dopamine receptor expression follows an inverted U trajectory, peaking in early adolescence before declining to adult levels [37]. This is accompanied by a steady increase in striatal dopamine turnover, synthesis and transporter density [6,12,38]. By contrast, dopamine receptors in the frontal cortex rise to reach adult levels by mid-adolescence, while dopamine turnover and synthesis peak before decreasing [6,12]. These regional changes appear to reflect a functional shift in the balance of mesocortical to mesolimbic dopaminergic activity as adolescence progresses [12], underscoring the malleability of the dopaminergic system during this epoch.

The serotonin system develops to near maturity early in life, with adult serotonergic innervation and serotonin synthesis capabilities obtained by the end of the third postnatal week in the rat [39]. However, maturational changes within the serotonin system occur throughout

adolescence. Serotonin levels and 5-HT_{1A} and 5-HT_{2A} receptor densities are elevated in the adolescent brain [6,39], while 5-HTT density and serotonin turnover is generally lower and increases towards adult levels as adolescence progresses [6,40].

Development of the norepinephrine system lags behind that of the serotonin system, with adult concentrations of norepinephrine not obtained until mid-adolescence in the rat [39]. Although somewhat variable between brain regions, the inverted U function is apparent for adrenergic receptors [41], synaptic density [39] and the norepinephrine transporter [42].

Maintaining the balance

Given the high levels of reorganization, growth and pruning occurring during adolescence both within and between brain systems, perturbations of the balance between these processes can have profound and lasting consequences. The adolescent brain is highly receptive to environmental signals, whether natural or synthetic, and becomes wired to match this input [14]. Adolescence is also a period of heightened susceptibility to stress [43] and development of psychopathologies [26] for which psychotropic drugs are the most common form of treatment. As such, it is vital to evaluate the safety and efficacy of such treatments in adolescent populations.

Antidepressant treatment of children & adolescents

Rates of antidepressant prescription have increased over the past two decades, with antidepressants now the most commonly prescribed class of medications in the USA [44]. Prescription of antidepressant drugs, particularly the SSRIs, also increased over this period in pediatric and adolescent populations [16,44], although declines followed the 2004 US FDA warnings on the hazards of antidepressant use in children and teenagers [45]. Despite these declines, approximately 2.5% of US children under the age of 18 years are thought to currently receive antidepressant drugs [44,45].

One factor driving these high rates of antidepressant prescription is the difficulty in finding effective treatments for depression in children and adolescents. While psychotherapeutic options such as cognitive–behavioral therapy and interpersonal therapy show some benefit [46], they tend to be slow to take effect and are less effective in cases of greater severity or with externalizing comorbid conditions [47,48]. TCAs and monoamine oxidase inhibitors (MAOIs) are not recommended in young people due to their unfavorable side-effect profile, cardiotoxicity, lack of efficacy and association with fatal overdose [48,49]. Consequently, the SSRIs and to a certain extent, SNRIs are widely used as first-line treatments for young people with depression.

The SSRI controversy

In recent years, the use of SSRIs in the treatment of childhood and adolescent depression and anxiety has become a topic of considerable debate. This debate is concerned with two issues, namely efficacy (i.e., SSRIs, with the possible exception of fluoxetine [50], appear to have minimal efficacy in young people with depressive disorders [51,52]) and safety (i.e., SSRIs may cause serious psychiatric side effects in children and adolescents, being associated with worsening of depression and increased risk of suicidal ideation and behavior [53–56], particularly during the early stages of treatment [57]). There are some indications that the SNRIs and TCAs may carry similar risks in adolescent populations [58].

Concerns about the safety of the SSRIs began in the early 1990s with several case reports detailing the emergence of suicidal preoccupation and deliberate self-harm in adults and young people treated with fluoxetine [59,60]. Subsequent investigations largely dismissed safety concerns in adults: many well-controlled studies revealed that, overall, adults treated with SSRIs had a similar or lower risk of suicidal ideation and attempts compared with those treated with placebo [53,54,61]. However, there is a recognition that as many as 50% of adult patients do not show a clinically significant response to SSRI treatment [62,63], and a subset are susceptible to treatment-emergent suicidality [54].

By contrast, concerns about pediatric suicidality due to SSRI treatment has intensified. In the late 1990s, the FDA requested well-controlled pediatric studies from the manufacturers of various antidepressants in an attempt to resolve the issue [301]. Although no completed suicides occurred in any of these studies, the FDA reviewers noted that many of the reports suggested an increased risk of suicidality among treated children and adolescents compared with placebo-treated controls. Furthermore, many of the studies reported little evidence of efficacy [301].

The most concerning findings, perhaps, were associated with the SSRI paroxetine. In 2001, a controversial and apparently ghostwritten paper published in the *Journal of the American Academy of Child and Adolescent Psychiatry* under

the authorship of Keller and colleagues presented the results of SmithKline Beecham's Study 329 on paroxetine in adolescent major depression (**Box 1**) [64]. Contrary to the misleading claims of the published paper that "paroxetine is generally well-tolerated and effective for major depression in adolescents" [65], Study 329 actually showed evidence of elevated rates of adverse effects, including suicidal ideation/gestures, worsening depression and aggression in paroxetine-treated adolescents. Furthermore, paroxetine failed to show efficacy on the two predefined primary measures. Later studies supported these initial findings [50,66,67]. In 2003, the FDA recommended against the use of paroxetine in depressed children and adolescents [68]. The UK Medicines and Healthcare Regulatory Agency (MHRA) took a more drastic approach, prohibiting its use entirely in those under 18 years of age [302].

Paroxetine was not the only antidepressant to show such effects. Although some studies demonstrated efficacy of sertraline [69] and citalopram [70] for the treatment of depression in young people, the majority showed no benefit over placebo [50,51,67]. Furthermore, elevated risk of suicidal ideation and other potentially related adverse effects (e.g., mania, hypomania, agitation and aggression) have been reported in pediatric trials involving sertraline, citalopram and fluvoxamine [55,61,71]. The only exception appears to be fluoxetine, which demonstrates efficacy in pediatric randomized controlled trials [72,73] and appears to be associated with a lower risk of suicide-related adverse effects than other SSRIs [50,55]. Consequently, fluoxetine is currently the only antidepressant approved for the treatment of depression in pediatric patients in the UK and USA [301]. Even so, questions remain about the safety and efficacy of fluoxetine in adolescent populations [74].

Although the pediatric use of all other SSRIs is contraindicated in the UK [303], the FDA stopped short of such a move in light of the limited treatments available for depression in young people. Instead, in 2004 the FDA introduced a black box warning on all SSRIs, notifying prescribers and consumers of the potential increased risk of suicidal ideation and behavior in people under 18 years of age [75]. This warning was modified in 2007 to include people aged 24 years and under, following evidence that the increased risk extends into young adulthood [54].

Nevertheless, the association between SSRIs and suicidality in pediatric patients remains uncertain. Although evidence from randomized controlled trials appears to point to a causal relationship, methodological shortcomings relating to sample selection [76,77] suggest that the results should be treated with caution. The rarity of suicide also necessitates the use of less definite measures of suicidality in these trials, such as attempts and ideation, which may not necessarily predict suicide completion [78]. In addition, some epidemiological studies suggest a negative relationship between SSRI prescription and suicide rates [76,79], although these claims are contested [78,80–82].

Box 1. Adolescents and paroxetine: misleading claims of Study 329.

- In 1992, Keller and colleagues formulated a proposal for a multicenter, randomized controlled trial comparing the selective serotonin-reuptake inhibitor paroxetine and the tricyclic antidepressant imipramine in adolescent major depression. SmithKline Beecham (SKB; now GlaxoSmithKline; producers of paroxetine [Paxil®]) accepted the proposal and the resulting study, Study 329, was completed in 1997 [201]. In 2001, the study was published in the *Journal of the American Academy of Child and Adolescent Psychiatry* with Keller as first author. The publication concludes: "The findings of this study provide evidence of the efficacy and safety of the selective serotonin-reuptake inhibitor, paroxetine, in the treatment of adolescent depression" [65].
- Following publication, however, the authenticity of these claims was questioned, and in 2004, various lawsuits were filed against SKB for misrepresentation of the efficacy and safety of paroxetine in young people [202,203]. These lawsuits led to disclosure of the contents of thousands of industry documents, the details of which are reviewed in detail elsewhere [201,203]. In summary, these internal documents revealed that "study 329 was negative for efficacy and positive for harm" [201].
- The study protocol specified two predefined primary outcome measures (change in Hamilton Depression Rating Scale score and proportion with Hamilton Depression Rating Scale score ≤8 or reduced by ≥50%) and six secondary measures, none of which reached significance for paroxetine compared with placebo. At least 19 additional measures were introduced following initial data analysis. Of these, only four gave positive results [201]. The final published study presents these outcomes as primary and depression-related outcome measures.
- The paper also reports the occurrence of 11 serious adverse effects in adolescents treated with paroxetine (compared with five and two in imipramine and placebo groups, respectively). Of these, ten were considered psychiatric events and five were grouped under the term 'emotional lability'. However, the authors concluded that only one of these serious adverse effects (headache) was related to treatment. By contrast, SKB's internal reports revealed that at least eight paroxetine-treated patients self-harmed or reported treatment-emergent suicidal ideation, and that most adverse effects were considered to be related or possibly related to treatment [201]. Despite these revelations, requests to the publishing journal for retraction of the article have been denied [203].
- Some have cited Study 329 as symptomatic of a larger problem within medical research, whereby widespread practices such as selective publishing [204] and medical ghostwriting [205,206] undermine the scientific ethic of objective reporting.

Overall, however, the evidence suggests that adults and young people respond differently to antidepressant drugs, with SSRIs less likely to show efficacy and more likely to lead to adverse psychiatric effects in those under 25 years of age. The mechanism underlying these effects is unknown, although pharmacokinetic differences [83] and increased susceptibility to activating side effects [84] have been suggested to play a role in the emergence of suicidal behavior. Studies investigating developmental differences in neural responses to antidepressants have provided additional clues. These studies will be reviewed in the following sections. Summaries of the key preclinical and pharmacogenomic findings are presented in Tables 1 & 2, respectively.

Neural effects of antidepressants in adolescents: considerations in reviewing the literature

Why animal studies?

Given the complications involved in the investigation of brain structure and function, it is not surprising that the majority of studies exploring developmental differences in neural effects of antidepressants have employed laboratory animals. In addition to this prime advantage, animal studies overcome many limitations associated with the use of clinical samples, such as attrition, prior, current and future treatment exposure, difficulties in cause–effect determination and the prohibitive time span of studies looking for long-term effects [14]. In addition, clinical trials often employ patients with a wide age range, limiting their ability to detect developmental differences [85]. By contrast, animal studies allow for examination of effects over a clearly restricted age range with key variables under strict experimental control.

Of course, the limitations of animal studies cannot be ignored. Extrapolation to the human condition can be complicated by species differences, dose selection and route of drug administration. These issues are of particular relevance when conducting developmental comparisons [12]. For example, age-related pharmacokinetic differences may produce dramatically different drug concentrations in the brain and plasma of adolescent rodents compared with those seen in adults given an equivalent dose [86,87]. Strain differences can also complicate conclusions drawn from animal studies as different strains often differ in baseline behavior and neurochemistry, as well as responsiveness to antidepressants and other drugs [88,89].

Regardless, adolescent rodents provide some surprising analogs of the behavioral response of young persons to antidepressants, generally displaying behaviors reflective of minimal efficacy and increased risk of adverse effects. For example, SSRI administration to adolescent rodents has been associated with increases in anxiety-like [90] and depression-like behaviors [87], minimal antidepressant-like effects (see Figure 1 [86]) and decreased sociability [86].

Normal animals versus animal models of depression

An additional advantage of animal studies is the ability to separate drug effects from the underlying disease state, allowing easier detection of adverse neural and behavioral effects [14]. For example, animal studies have an important role to play in resolving the recent controversy on the role of antipsychotic drugs in the regional brain atrophy observed in schizophrenic patients [91]. Similarly, studies employing 'normal' animals can help to disentangle the effects of antidepressant drug exposure from the effects of the underlying depressive or anxious states. Furthermore, although most people who are prescribed antidepressants suffer from a mood disorder, a significant proportion of prescriptions are for alternative diagnoses such as anxiety disorders, eating disorders, substance abuse, dementia, headache, fibromyalgia and chronic pain [92,93]. Concerns about off-label prescribing, overdiagnosis and overprescription [94] suggest the use of 'normal' animals may be increasingly relevant to the clinical situation.

Nonetheless, the primary aim of therapeutic drugs is to normalize aberrant behavior and/or brain function, and this cannot be examined in normal animals [14]. Animal models of depression have been developed in an attempt to reflect the etiology of depression and its neural correlates. Given the association between stressful life events and the development of depression in humans (see [95,96] for reviews), many paradigms expose standard or genetically susceptible strains to early-life or chronic stress [97]. Use of such models facilitates detection of interaction effects occurring between the disease state and the drug treatment, whereby the treatment has one effect in a model of depression and an opposite (or null) effect in normal animals (e.g., [98]). The use of a combination of animal models, normal animals and clinical studies is needed to obtain a full picture of drug actions.

Timing of drug administration & outcome assessment

Critical or sensitive periods are time-limited windows when development requires, or is strongly influenced by, certain environmental

Table 1. Preclinical literature investigating the neural responses to antidepressants in adolescent rodents.

Study	Measure	Species and strain	Age during drug administration	Sex	Drug and route of administration	Duration	Washout	Results: adolescent	Results: adult	Ref.
Serotonergic function										
Karanges *et al.*	5-HT and metabolites	W rat	Adolescent (P28–49) Adult (P70–91)	M	10 mg/kg PRX (drinking water)	22 d	None	↓ striatal 5-HIAA, 5-HT turnover ↔ striatal 5-HT	↓ striatal 5-HIAA, 5-HT turnover ↔ striatal 5-HT	[86]
Karanges *et al.*	5-HTT binding	W rat	Adolescent (P28–49) Adult (P70–91)	M	10 mg/kg PRX (drinking water)	22 d	5 d	↑ 5-HTT (BLA) ↔ 5-HTT (CA3)	↔ 5-HTT (BLA, CA3)	[86]
Wegerer *et al.*	5-HTT binding/affinity	W rat	Early adolescent (P25–40) Late adolescent (P50–65)	M	5 mg/kg FLX (drinking water)	14 d	10 d (early) 25 d (late)	↑ 5-HTT binding (FC) in early adolescent ↔ 5-HTT binding (PC, OC, HYP, MB) in early adolescent ↔ 5-HTT binding in late adolescent ↔ 5-HTT affinity	–	[105]
Wegerer *et al.*	5-HTT binding/affinity	W rat	Early adolescent (P25–40)	M	5 mg/kg FLX (drinking water)	14 d	50 d	↑ 5-HTT binding (FC) ↔ 5-HTT binding (PC, OC HYP, MB) ↔ 5-HTT affinity	–	[105]
Homberg *et al.*	5-HT_{1A}-R binding	WU rat	Adolescent (P25–49) Adult (P67–88)	M	12 mg/kg FLX (oral gavage)	21 d	14–17 d	↔ 5-HT_{1A}	↔ 5-HT_{1A}	[125]
de Jong *et al.*	5-HT_{1A}-R function via 8-OH-DPAT challenge	W rat	Adolescent (P33–62)	M	15 mg/kg PRX; 30 mg/kg FLV	30 d	14 w	↔ Sexual behavior, lower lip retraction	–	[123]
Landry *et al.*	5-HT_{2A}-R function via ± DOI challenge	SD rat	Adolescent (P35–49)	M	10 mg/kg FLX (ip.)	14 d	None	↓ oxytocin release ↔ ACTH, Cort, PRA, PRC	–	[124]
Bhansali *et al.*	*5-HT$_{2C}$* mRNA pre-editing	BALB/cJ mice (SFR/IMS)	Adolescent (P32–61) Adult (P60–88)	M/F	7.5–16 mg/kg (adolescent) 16 mg/kg (adult) FLX (drinking water)	28 d	1 d	↑ *5-HT$_{2C}$* mRNA pre-editing (↑ expression of 5-HT_{2C}-R with reduced function) (SFR) ↓ *5-HT$_{2C}$* mRNA pre-editing (IMS) ↓ *5-HT$_{2C}$* mRNA pre-editing increase in response to adult stress (IMS) ↔ cytoplasmic *5-HT$_{2C}$-R* mRNA concentration (SFR/IMS) ↓ *Gαq* mRNA (IMS) ↔ *Gαq* mRNA (SFR)	↔ *5-HT$_{2C}$* mRNA pre-editing or cytoplasmic *5-HT$_{2C}$-R* mRNA (IMS) ↔ *Gαq* mRNA (SFR) ↓ *Gαq* mRNA/protein (IMS)	[130]

↔: No difference versus controls; ↑: Increase; ↓: Decrease; (↑): Trend toward increase versus controls ($p < 0.07$); (↓): Trend toward decrease versus controls ($p < 0.07$); 5-HIAA: 5-hydroxyindoleacetic acid; 5-HT: 5-hydroxytryptamine; 5-HTT: Serotonin transporter; ACTH: Adrenocorticotropic hormone; Amyg: Amygdala; BDNF: Brain-derived neurotrophic factor; b.i.d.: Twice daily; BLA: Basolateral amygdala; CA1: CA1 region of the hippocampus; CA3: CA3 region of the hippocampus; Cort: Corticosterone; CPu: Caudate putamen; CREB: cAMP response element-binding protein; d: Day; DA: Dopamine; DAT: Dopamine transporter; DG: Dentate gyrus; DMI: Desipramine; DOPAC: 3,4-dihydroxyphenylacetic acid; DRN: Dorsal raphe nucleus; egr-3*: Early growth response gene 3; ERK2: Extracellular signal-regulated kinase 2; ESC: Escitalopram; F: Female; FC: Frontal cortex; FLV: Fluvoxamine; FLX: Fluoxetine; Glu:Cr: Glutamate:creatine ratio; HIPP: Hippocampus; HVA: Homovanillic acid; HYP: Hypothalamus; IMS: Infant maternal separation; int.: Significant age versus treatment interaction effect; ip.: Intraperitoneal; M: Male; m: Month; MB: Midbrain; MI:Cr: Myo-inositol:creatine ratio; mPFC: Medial prefrontal cortex; NAA:Cr: N-acetylaspartate:creatine ratio; NAcc: Nucleus accumbens; NE: Norepinephrine; NET: Norepinephrine transporter; OC: Occipital cortex; P: Postnatal day; PC: Parietal cortex; PRA: Plasma renin activity; PRC: Plasma renin concentration; PRX: Paroxetine; PSA-NCAM: Polysialylated from of the neural cell adhesion molecule; R: Right; SD: Sprague–Dawley; Ser: Sertraline; SFR: Standard facility reared; SIR: Social isolation rearing; SS: Social stress; STR: Striatum; SW: Swiss Webster; TIAN: Tianeptine; VEN: Venlafaxine; VTA: Ventral tegmental area; W: Wistar; w: Week; WU: Wistar Unilever; zif268: Early growth response protein-1.*

Table 1. Preclinical literature investigating the neural responses to antidepressants in adolescent rodents (cont.).

Study	Measure	Species and strain	Age during drug administration	Sex	Drug and route of administration	Duration	Washout	Results: adolescent	Results: adult	Ref.
Serotonergic function (cont.)										
Carrey *et al.*	Fenfluramine challenge	SD rat	Early adolescent (P20–39) Late adolescent (P40–59) Adult (P80–100)	M	2, 10 mg/kg SER (ip.)	14 d	5 d	↔ prolactin at 2, 10 mg/kg	↓ prolactin at 2, 10 mg/kg	[85]
Dopaminergic function										
Karanges *et al.*	DA and metabolites	W rat	Adolescent (P28–49) Adult (P70–91)	M	10 mg/kg PRX (drinking water)	22 d	None	↔ striatal DA, HVA, DA turnover (↓) DOPAC (int.)	↑ striatal HVA, DA turnover ↔ DA (↑) DOPAC (int.)	[86]
Karanges *et al.*	DAT	W rat	Adolescent (P28–49) Adult (P70–91)	M	10 mg/kg PRX (drinking water)	22 d	5 d	↔ DAT (NAcc, medial/lateral CPu)	↓ DAT (NAcc) ↔ DAT (medial/lateral CPu)	[86]
Noradrenergic function										
Karanges *et al.*	NE	W rat	Adolescent (P28–49) Adult (P70–91)	M	10 mg/kg PRX (drinking water)	22 d	None	↔ NE	↔ NE	[86]
Wegerer *et al.*	NET binding/affinity	W rat	Early adolescent (P25–40) Late adolescent (P50–65)	M	5 mg/kg FLX (drinking water)	14 d	10, 50 d (early) 25 d (late)	↔ NET binding/affinity	–	[105]
West *et al.*	Locus coeruleus activity	SD rat	Adolescent (P45–58) Adult (5+ m)	M	0.625, 1.25, 2.5, 5 mg/kg PRX (minipump)	2, 4, 8, 14 d	None	↑ spontaneous firing/sensory-evoked firing at 1.25, 2.5 mg/kg (2, 4 d) ↓ spontaneous firing at 5 mg/kg (2 d) ↓ spontaneous firing/sensory-evoked firing at all tested doses (8, 14 d)	↓ spontaneous firing/sensory-evoked firing at 2.5 mg/kg (after 2 d); 2.5, 5 mg/kg (4 d); all tested doses (8, 14 d)	[87]
West *et al.*	Locus coeruleus activity	SD rat	Adolescent (P45–48)	M	10 mg/kg VEN 2.5 mg/kg DMI (minipump)	4 d	None	↑ spontaneous firing/sensory-evoked firing (VEN) ↓ spontaneous firing/sensory-evoked firing (DMI)	–	[143]

↔: No difference versus controls; ↑: Increase; ↓: Decrease; (↑): Trend toward increase versus controls ($p < 0.07$); (↓): Trend toward decrease versus controls ($p < 0.07$); 5-HIAA: 5-hydroxyindoleacetic acid; 5-HT: 5-hydroxytryptamine; 5-HTT: Serotonin transporter; ACTH: Adrenocorticotropic hormone; Amyg: Amygdala; BDNF: Brain-derived neurotrophic factor; b.i.d.: Twice daily; BLA: Basolateral amygdala; CA1: CA1 region of the hippocampus; CA3: CA3 region of the hippocampus; Cort: Corticosterone; CPu: Caudate putamen; CREB: cAMP response element-binding protein; d: Day; DA: Dopamine; DAT: Dopamine transporter; DG: Dentate gyrus; DMI: Desipramine; DOPAC: 3,4-dihydroxyphenylacetic acid; DRN: Dorsal raphe nucleus; egr-3*: Early growth response gene 3; ERK2: Extracellular signal-regulated kinase 2; ESC: Escitalopram; F: Female; FC: Frontal cortex; FLV: Fluvoxamine; FLX: Fluoxetine; Glu:Cr: Glutamate:creatine ratio; HIPP: Hippocampus; HVA: Homovanillic acid; HYP: Hypothalamus; IMS: Infant maternal separation; int.: Significant age versus treatment interaction effect; ip.: Intraperitoneal; M: Male; m: Month; MB: Midbrain; MI:Cr: Myo-inositol:creatine ratio; mPFC: Medial prefrontal cortex; NAA:Cr: N-acetylaspartate:creatine ratio; NAcc: Nucleus accumbens; NE: Norepinephrine; NET: Norepinephrine transporter; OC: Occipital cortex; P: Postnatal day; PC: Parietal cortex; PRA: Plasma renin activity; PRC: Plasma renin concentration; PRX: Paroxetine; PSA-NCAM: Polysialylated from of the neural cell adhesion molecule; R: Right; SD: Sprague–Dawley; Ser: Sertraline; SFR: Standard facility reared; SIR: Social isolation rearing; SS: Social stress; STR: Striatum; SW: Swiss Webster; TIAN: Tianeptine; VEN: Venlafaxine; VTA: Ventral tegmental area; W: Wistar; w: Week; WU: Wistar Unilever; zif268: Early growth response protein-1.*

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Neurogenesis and plasticity										
Hodes *et al.*	Adult hippocampal neurogenesis	SD rat	Peripubertal (P24–40) Adult (P63–90)	M/F	5 mg/kg FLX (ip.)	14–18 d	1, 2, 29 d	↔ DNA synthesis; cell proliferation (M/F) ↔ cell survival (M) (↓) cell survival (F)	↑ DNA synthesis; cell proliferation (M) ↔ cell survival (M) ↔ DNA synthesis, cell proliferation, cell survival (F)	[161]
Cowen *et al.*	Adult hippocampal neurogenesis	SD rat	Adolescent (P28–52) Adult (P70–94) Aged (12 m)	M	5 mg/kg FLX (ip.)	25 d	1 d	↔ DG volume ↔ cell proliferation/survival	↔ DG volume ↔ cell proliferation/ survival	[28]
Oh *et al.*	Adult hippocampal neurogenesis	SW mice	Juvenile (P14–42)	M	3 mg/kg FLX (minipump + drinking water)	28 d	None	↔ cell proliferation	–	[90]
Navailles *et al.*	Adult hippocampal neurogenesis	C57Bl/6J, BALB/cJ mice (SFR/IMS)	Adolescent (P32–56) Adult (P60–84)	M/F	10, 16, 25 mg/kg FLX (drinking water)	24 d	0, 14 d	↑ cell proliferation, survival, differentiation (C57Bl/6J at 16, 25 mg/kg after SFR) ↑ cell proliferation (BALB/cJ at 16, 25 mg/kg after SFR) ↔ cell survival, differentiation (BALB/cJ at 16, 25 mg/kg after SFR) ↔ cell proliferation, survival, differentiation (C57Bl/6J, BALB/cJ at 16, 25 mg/kg after IMS)	↔ cell proliferation, survival, differentiation (C57Bl/6J, BALB/cJ at 10, 16, 25 mg/kg) after IMS/SFR	[98]
Ibi *et al.*	Adult hippocampal neurogenesis	Mouse (SIR/SFR)	Adolescent (P24–37)	M	10 mg/kg FLX (ip.)	14 d	None	↑ cell survival and NeuN-positive cells (DG) (SIR) ↔ cell survival (DG) (SFR)	–	[159]
Kozisek *et al.*	*BDNF*, *TrkB* mRNA	Rat	Prepubertal (P24–28) Adult		10, 15 mg/kg ESC, DMI (ip. b.i.d.)	4 d	12–14 h	↔ *TrkB* mRNA, *BDNF* mRNA/protein	↔ *TrkB* mRNA, *BDNF* mRNA/ protein	[160]

↔: No difference versus controls; ↑: Increase; ↓: Decrease; (↑): Trend toward increase versus controls ($p < 0.07$); (↓): Trend toward decrease versus controls ($p < 0.07$); 5-HIAA: 5-hydroxyindoleacetic acid; 5-HT: 5-hydroxytryptamine; 5-HTT: Serotonin transporter; ACTH: Adrenocorticotropic hormone; Amyg: Amygdala; BDNF: Brain-derived neurotrophic factor; b.i.d.: Twice daily; BLA: Basolateral amygdala; CA1: CA1 region of the hippocampus; CA3: CA3 region of the hippocampus; Cort: Corticosterone; CPu: Caudate putamen; CREB: cAMP response element-binding protein; d: Day; DA: Dopamine; DAT: Dopamine transporter; DG: Dentate gyrus; DMI: Desipramine; DOPAC: 3,4-dihydroxyphenylacetic acid; DRN: Dorsal raphe nucleus; egr-*3: Early growth response gene 3; ERK2: Extracellular signal-regulated kinase 2; ESC: Escitalopram; F: Female; FC: Frontal cortex; FLV: Fluvoxamine; FLX: Fluoxetine; Glu:Cr: Glutamate:creatine ratio; HIPP: Hippocampus; HVA: Homovanillic acid; HYP: Hypothalamus; IMS: Infant maternal separation; int.: Significant age versus treatment interaction effect; ip.: Intraperitoneal; M: Male; m: Month; MB: Midbrain; MI:Cr: Myo-inositol:creatine ratio; mPFC: Medial prefrontal cortex; NAA:Cr: N-acetylaspartate:creatine ratio; NAcc: Nucleus accumbens; NE: Norepinephrine; NET: Norepinephrine transporter; OC: Occipital cortex; P: Postnatal day; PC: Parietal cortex; PRA: Plasma renin activity; PRC: Plasma renin concentration; PRX: Paroxetine; PSA-NCAM: Polysialylated from of the neural cell adhesion molecule; R: Right; SD: Sprague–Dawley; Ser: Sertraline; SFR: Standard facility reared; SIR: Social isolation rearing; SS: Social stress; STR: Striatum; SW: Swiss Webster; TIAN: Tianeptine; VEN: Venlafaxine; VTA: Ventral tegmental area; W: Wistar; w: Week; WU: Wistar Unilever; zif268: Early growth response protein-1.*

Table 1. Preclinical literature investigating the neural responses to antidepressants in adolescent rodents (cont.).

Study	Measure	Species and strain	Age during drug administration	Sex	Drug and route of administration	Duration	Washout	Results: adolescent	Results: adult	Ref.
Neurogenesis and plasticity (cont.)										
Warren *et al.*	BDNF and related signaling molecules	SD rat	Peripubertal (P20–34)	M	2.5 mg/kg FLX (ip. b.i.d.)	15 d	1 d	↓ *ERK2*, *CREB* mRNA ↑ *mTOR* mRNA ↔ *BDNF*, *c-fos*, *zif268* mRNA (VTA)	–	[104]
Warren *et al.*	BDNF and related signaling molecules	SD rat	Peripubertal (P20–34)	M	2.5 mg/kg FLX (ip. b.i.d.)	15 d	60 d	↓ *BDNF* mRNA ↔ *ERK2*, *CREB*, *mTOR*, *c-fos*, *zif268* mRNA (VTA)	–	[104]
Homberg *et al.*	Synaptic remodeling via PSA-NCAM expression	WU rat	Peripubertal (P25–49) Adult (P67–88)	M	12 mg/kg FLX (oral gavage)	21 d	14–17 d	(↑) PSA-NCAM (Amyg) ↔ PSA-NCAM (DRN, mPFC)	(↓) PSA-NCAM (Amyg) ↔ PSA-NCAM (DRN, mPFC)	[125]
Leussis *et al.*	Synaptic plasticity via synaptophysin expression	SD rat (SS/SFR)	Adolescent (P40–55)	M	10 mg/kg TIAN (ip.)	16 d	5 d	↑ synaptophysin (HIPP) after SFR ↔ synaptophysin (HIPP) after SS ↔ synaptophysin (PFC, STR) after SFR/SS	–	[163]
Norrholm and Ouimet	Dendritic spine density	SD rat	Juvenile (P21)	M	5 mg/kg FLX, 5 mg/kg FLV (ip.)	1 d	1 d	↑ dendritic spine density (CA1, DG) with FLV ↔ dendritic spine density (CA1, DG) with FLX ↔ secondary dendrite length (CA1, DG) with FLV, FLX ↑ secondary dendrites (CA1) with FLX ↑ summed dendritic lengths (CA1) with FLX, FLV	–	[30]

↔: No difference versus controls; ↑: Increase; ↓: Decrease; (↑): Trend toward increase versus controls ($p < 0.07$); (↓): Trend toward decrease versus controls ($p < 0.07$); 5-HIAA: 5-hydroxyindoleacetic acid; 5-HT: 5-hydroxytryptamine; 5-HTT: Serotonin transporter; ACTH: Adrenocorticotropic hormone; Amyg: Amygdala; BDNF: Brain-derived neurotrophic factor; b.i.d.: Twice daily; BLA: Basolateral amygdala; CA1: CA1 region of the hippocampus; CA3: CA3 region of the hippocampus; Cort: Corticosterone; CPu: Caudate putamen; CREB: cAMP response element-binding protein; d: Day; DA: Dopamine; DAT: Dopamine transporter; DG: Dentate gyrus; DMI: Desipramine; DOPAC: 3,4-dihydroxyphenylacetic acid; DRN: Dorsal raphe nucleus; egr-3: Early growth response gene 3; ERK2: Extracellular signal-regulated kinase 2; ESC: Escitalopram; F: Female; FC: Frontal cortex; FLV: Fluvoxamine; FLX: Fluoxetine; Glu:Cr: Glutamate:creatine ratio; HIPP: Hippocampus; HVA: Homovanillic acid; HYP: Hypothalamus; IMS: Infant maternal separation; int.: Significant age versus treatment interaction effect; ip.: Intraperitoneal; M: Male; m: Month; MB: Midbrain; MI:Cr: Myo-inositol:creatine ratio; mPFC: Medial prefrontal cortex; NAA:Cr: N-acetylaspartate:creatine ratio; NAcc: Nucleus accumbens; NE: Norepinephrine; NET: Norepinephrine transporter; OC: Occipital cortex; P: Postnatal day; PC: Parietal cortex; PRA: Plasma renin activity; PRC: Plasma renin concentration; PRX: Paroxetine; PSA-NCAM: Polysialylated from of the neural cell adhesion molecule; R: Right; SD: Sprague–Dawley; Ser: Sertraline; SFR: Standard facility reared; SIR: Social isolation rearing; SS: Social stress; STR: Striatum; SW: Swiss Webster; TIAN: Tianeptine; VEN: Venlafaxine; VTA: Ventral tegmental area; W: Wistar; w: Week; WU: Wistar Unilever; zif268: Early growth response protein-1.

Table 1. Preclinical literature investigating the neural responses to antidepressants in adolescent rodents (cont.).

Study	Measure	Species and strain	Age during drug administration	Sex	Drug and route of administration	Duration	Washout	Results: adolescent	Results: adult	Ref.
Neurogenesis and plasticity (cont.)										
Norrholm and Ouimet	Dendritic spine density	SD rat	Juvenile (P21–P42)	M	5 mg/kg FLX, 5 mg/kg FLV (ip.)	21 d	1, 21 d	↓ dendritic spine density (CA1) with FLX ↔ dendritic spine density (DG) with FLX, FLV ↔ secondary dendrites, length secondary dendrites, summed dendritic length (CA1) with FLX, FLV	–	[30]
Hui *et al.*	HIPP integrity	SD rat (IMS/SFR)	Adolescent (P43–60)	M/F	10 mg/kg ESC (oral gavage)	17 d	10–15 d	↔ HIPP volume (M/F) ↑ NAA:Cr (R HIPP) for SFR/IMS ↑ Glu:Cr (R HIPP), MI:Cr (bilateral) for IMS only	–	[171]
Hodes *et al.*	Cort	SD rat	Peripubertal (P24–40) Adult (P63–90)	M/F	5 mg/kg FLX (ip.)	14–18 d	1 d	↔ Cort (M/F)	↔ Cort (M/F)	[161]
Hodes *et al.*	Cort	SD rat	Peripubertal (P24–40) Adult (P63–90)	M/F	5 mg/kg FLX (ip.)	14–18 d	29 d	↔ Cort (M) ↓ Cort (F)	↔ Cort (M/F)	[161]
Landry *et al.*	Cort	SD rat	Adolescent (P35–49)	M	10 mg/kg FLX (ip.)	14 d	None	↔ basal ACTH, Cort	–	[124]
Other										
Bhansali *et al.*	*$GABA_A$-R* mRNA, *egr-3* mRNA	BALB/cJ mice (SFR/IMS)	Adolescent (P32–61) Adult (P60–88)	M/F	7.5–16 mg/kg (adolescent) 16 mg/kg (adult) FLX (drinking water)	28 d	1 d	↓ *$GABA_A$-R α1* subunit mRNA (IMS) ↔ *$GABA_A$-R α1* subunit mRNA (SFR) ↓ *egr-3* mRNA (IMS) ↑ *egr-3* mRNA (SFR)	↔ *$GABA_A$-R α1* subunit mRNA (IMS/SFR) ↔ *egr-3* mRNA (IMS/SFR)	[130]
Landry *et al.*	Neuropeptides	SD rat	Adolescent (P35–49)	M	10 mg/kg FLX (ip.)	14 d	None	↔ basal plasma oxytocin, PRA, PRC	–	[124]

↔: No difference versus controls; ↑: Increase; ↓: Decrease; (↑): Trend toward increase versus controls ($p < 0.07$); (↓): Trend toward decrease versus controls ($p < 0.07$); 5-HIAA: 5-hydroxyindoleacetic acid; 5-HT: 5-hydroxytryptamine; 5-HTT: Serotonin transporter; ACTH: Adrenocorticotropic hormone; Amyg: Amygdala; BDNF: Brain-derived neurotrophic factor; b.i.d.: Twice daily; BLA: Basolateral amygdala; CA1: CA1 region of the hippocampus; CA3: CA3 region of the hippocampus; Cort: Corticosterone; CPu: Caudate putamen; CREB: cAMP response element-binding protein; d: Day; DA: Dopamine; DAT: Dopamine transporter; DG: Dentate gyrus; DMI: Desipramine; DOPAC: 3,4-dihydroxyphenylacetic acid; DRN: Dorsal raphe nucleus; egr-3*: Early growth response gene 3; ERK2: Extracellular signal-regulated kinase 2; ESC: Escitalopram; F: Female; FC: Frontal cortex; FLV: Fluvoxamine; FLX: Fluoxetine; Glu:Cr: Glutamate:creatine ratio; HIPP: Hippocampus; HVA: Homovanillic acid; HYP: Hypothalamus; IMS: Infant maternal separation; int.: Significant age versus treatment interaction effect; ip.: Intraperitoneal; M: Male; m: Month; MB: Midbrain; MI:Cr: Myo-inositol:creatine ratio; mPFC: Medial prefrontal cortex; NAA:Cr: N-acetylaspartate:creatine ratio; NAcc: Nucleus accumbens; NE: Norepinephrine; NET: Norepinephrine transporter; OC: Occipital cortex; P: Postnatal day; PC: Parietal cortex; PRA: Plasma renin activity; PRC: Plasma renin concentration; PRX: Paroxetine; PSA-NCAM: Polysialylated from of the neural cell adhesion molecule; R: Right; SD: Sprague–Dawley; Ser: Sertraline; SFR: Standard facility reared; SIR: Social isolation rearing; SS: Social stress; STR: Striatum; SW: Swiss Webster; TIAN: Tianeptine; VEN: Venlafaxine; VTA: Ventral tegmental area; W: Wistar; w: Week; WU: Wistar Unilever; zif268: Early growth response protein-1.*

Table 2. Pharmacogenetic studies of antidepressant response in children and adolescents.

Study	Gene of interest	Population	Treatment	Results	Ref.
Brent *et al.*	*FKBP5* + 11 others	176 adolescents with treatment-resistant MDD (12–18 y) in the TORDIA study	SSRI (FLX, PRX, CIT) or VEN or SSRI + CBT or VEN + CBT	*FKBP5 rs1360780TT, rs3800373GG* genotypes (subsensitivity of glucocorticoid receptor) associated with suicidal events No associations with treatment response (including *TPH2*, *5-HTT*)	[183]
Joyce *et al.*	*5-HTT* *GNβ3*	169 depressed patients (mean age: 31.8 y)	NOR, FLX for 6 w	*5-HTTLPR ss* genotype associated with lower treatment response in patients aged ≥25 y (FLX, NOR) No association with treatment response in patients aged <25 y *GNβ3 T* allele associated with poorer treatment response in patients aged <25 y (NOR only)	[184]
Kronenberg *et al.*	*5-HTT*	74 treatment-naive out-patients with MDD and/or anxiety disorder (7–18 y)	CIT (10 mg x 1 w, then 20 mg x 2 w, then 20–40 mg) for up to 8 w	*5-HTTLPR ss* genotype associated with less symptom improvement on CDRS-R scale (depression), higher rates of suicidal ideation, lower rates of agitation	[182]
Rotberg *et al.*	*5-HTT* *TPH2*	83 children and adolescents with depression and anxiety disorders	CIT for 8 w	*5-HTTLPR s* allele associated with lower remission rate *TPH2 T* allele associated with lower remission rate (trend only) *5-HTTLPR L* allele + *TPH2 G* allele most likely to remit *5-HTTLPR s* allele + *TPH2 T* allele least likely to remit	[181]
Baumer *et al.*	*5-HTT*	47 children and adolescents with bipolar disorder or subthreshold mania	Retrospective assessment of prior reactions to antidepressant treatment	*5-HTTLPR* genotype not associated with antidepressant-induced mania	[185]

5-HTT: Serotonin transporter; 5-HTTLPR*: Serotonin-transporter-linked polymorphic region; CBT: Cognitive–behavioral therapy; CDRS-R: Children's Depression Rating Scale – Revised; CIT: Citalopram; FLX: Fluoxetine;* GNβ3*: G protein β3 subunit; MDD: Major depressive disorder; NOR: Nortriptyline; PRX: Paroxetine; SSRI: Selective serotonin-reuptake inhibitor; TORDIA: Treatment of SSRI-Resistant Depression in Adolescents; TPH2: Tryptophan hydroxylase 2; VEN: Venlafaxine; w: Week; y: Year.*

factors [6,14]. The timing of a critical or sensitive period is influenced by the developmental trajectory of the affected system, and even small shifts in timing may dramatically alter the behavioral or neural effects of a drug. Indeed, a shift of timing by 1 week during a key period of noradrenergic development alters the antidepressant-like response of rats to TCAs from nonresponsive at P21 to responsive at P28 [99].

Equally important is the timing of outcome assessment. Conclusions regarding beneficial and/or adverse effects of adolescent drug exposure will differ depending on whether the outcomes are assessed during treatment, shortly after treatment cessation or following an extended phase of drug washout. Andersen and Navalta propose an elegant model describing the 'equal, but opposite' enduring effects of developmental drug exposure [13,14,100]: although a drug may produce similar short-term effects in the developing and adult brain (e.g., the inhibition of 5-HTT by SSRIs), the enduring effects on the developing system may well be opposite to those seen during treatment in adults. Such enduring 'opposite' behavioral and neural effects are clearly seen following *in utero* or early life 5-HTT blockade [3,101,102]. Similar consequences may conceivably occur following alteration of maturational processes by adolescent

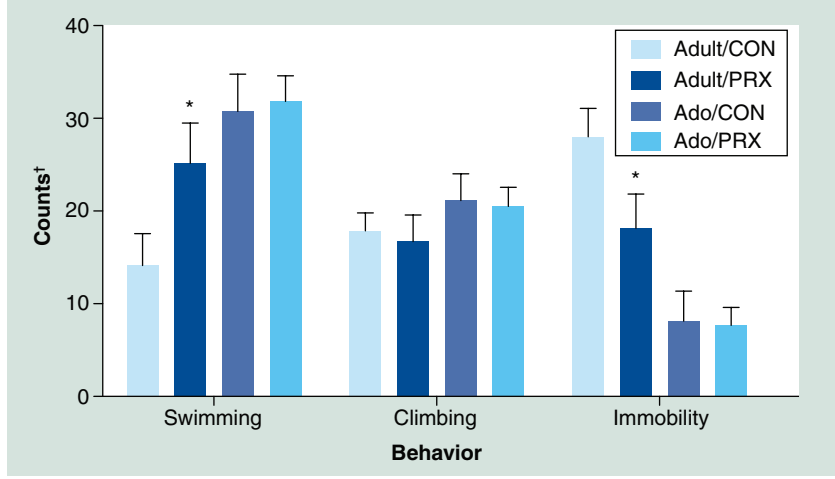

Figure 1. Effects of paroxetine (10 mg/kg in drinking water for 22 days) on depression-like behavior in the forced swim test in adolescent and adult rats.
†The number of 5-s intervals throughout the 5-min test period in which the specified behavior (swimming, climbing or immobility) is the dominant behavior.
*Significant treatment effect compared with age-matched controls ($p < 0.05$).
Ado: Adolescent; CON: Control; PRX: Paroxetine.
Adapted with permission from [86].

drug exposure. Indeed, unlike the anxiolytic effects of adult antidepressant treatment [103], SSRI exposure during adolescence appears to have anxiogenic consequences in adulthood [104]. Similarly, as described in the 'Serotonin system' section, the enduring increases in 5-HTT expression following developmental SSRI exposure contrast with the decreases in expression normally observed during treatment in adults [105,106].

Choice of antidepressant drug: differences between SSRIs

Despite their similarities, the SSRIs differ markedly from one another in pharmacokinetic and pharmacological profiles, and therefore in their efficacy, safety and suitability for clinical and animal studies. For example, the relative safety of fluoxetine in adolescents has been attributed to its long half-life and active metabolite, while paroxetine's short half-life has been implicated in its association with treatment-emergent suicidality [107]. Half-life is also a consideration in animal studies using once- or twice-daily drug administration, where a short half-life may prevent attainment of the steady-state levels needed for the detection of neural effects [108]. By contrast, many pharmacogenomic studies favor citalopram or escitalopram for its selectivity for the 5-HTT and limited interaction with the liver cytochrome P450 system [109].

Neural effects of antidepressants in adolescent animals

Effects on major neurotransmitter systems

Serotonin system

Interest in the role of 5-HT in depression and the antidepressant response began in the 1960s following the discovery of the serotonergic effects of the TCAs [110] and was heightened following the development of the SSRIs. While it is now generally accepted that there is no simple relationship between serotonergic dysfunction and depression [111], 5-HT remains a major research interest due to its involvement in the regulation of mood, emotional processing, appetite and sleep, all of which are disrupted in depression [111,112], and its importance in the mechanism of action of the SSRIs.

The effects of the SSRIs on the serotonergic system during adulthood are generally well characterized. 5-HTT, the primary target of the SSRIs, controls the intensity and duration of 5-HT signaling, being responsible for the reuptake of synaptic 5-HT into the presynaptic neuron. Upon administration, SSRIs bind 5-HTT with high affinity, inhibiting reuptake and increasing the synaptic concentration of 5-HT. However, increases in synaptic 5-HT are rapidly attenuated by homeostatic activation of 5-HT_{1A} and 5-HT_{1B} autoreceptors [113]. Therefore, lasting alterations in serotonergic tone may not occur until these receptors become desensitized 2–3 weeks later [114].

In addition to 5-HT_{1A} and 5-HT_{1B} autoreceptor desensitization, chronic SSRI treatment in adults has frequently been associated with desensitization and/or downregulation of other receptor subtypes including 5-HT_{2A} [115,116], 5-HT_{2C} [117] and 5-HT_{4} receptors [116]. Downregulation of 5-HTT is also often observed [106,108], although some studies report no difference from controls [118]. The reduction in the activity of 5-HT receptors and 5-HTT has been used to explain the delayed therapeutic response to SSRIs [119], although additional adaptive mechanisms are likely involved. Reductions in 5-HT turnover and in concentrations of the 5-HT metabolite 5-hydroxyindoleacetic acid also accompany chronic SSRI treatment in adults [86,120].

Studies in adolescent animals suggest that some components of the developing serotonergic system respond to SSRI treatment in a similar fashion to the adult system. For example, chronic (over 22 days) paroxetine had similar effects on whole-tissue concentrations of 5-HT (unchanged), 5-hydroxyindoleacetic acid (reduced) and 5-HT turnover (reduced) in the striatum of adult and adolescent rats (see Figure 2 [86]). However, the majority of studies describe age-specific effects of SSRIs on this system.

Two separate groups have investigated SSRI-induced changes in 5-HTT density in various regions of the adolescent rat brain following chronic SSRI administration. In contrast to the often-found decrease or null effect on 5-HTT binding density observed in adults, both studies report regional increases in 5-HTT binding in their younger cohort. An early study by Wegerer *et al.* reported increased levels of 5-HTT in the frontal cortex of early adolescent (P25) rats treated with fluoxetine for 14 days, with no alterations in binding density in the parietal cortex, occipital cortex, midbrain or hypothalamus [105]. Interestingly, no such effects were found in rats when treatment was started at P50, pointing to a sensitive period during early adolescent life. Karanges *et al.* reported similar findings, showing upregulation of 5-HTT in the amygdala, but not the hippocampus, in adolescent rats following chronic paroxetine treatment [86]. The frontal cortex and amygdala both

receive serotonergic innervation from the raphe nucleus [121], suggesting that these findings may reflect regional increases in serotonergic innervation and synaptic outgrowth rather than a direct increase in 5-HTT expression. Indeed, given the extensive remodeling and strengthening of connections occurring during adolescence and the role of 5-HT in synaptic outgrowth during development [101,122], such an explanation is plausible.

Interestingly, Wegerer *et al.* provide evidence that the regional increases in 5-HTT density endure into adult life [105], in contrast to the rapid recovery of SSRI-induced 5-HTT downregulation in adults [119]. Lasting changes in 5-HTT may explain the increases in anxiety-like behavior and sexual dysfunction observed in adult rats that have been treated with SSRIs during adolescence [123].

Several studies exploring the effects of SSRIs on 5-HT receptor function in adolescents have employed neuroendocrine or behavioral drug challenge techniques. In a study investigating the effects of chronic sertraline on serotonergic function, treated adult rats displayed the usual suppression of prolactin release to fenfluramine challenge, suggesting desensitization of postsynaptic serotonergic receptors in response to sertraline [85]. By contrast, the response to fenfluramine challenge was not altered by sertraline in prepubertal or peripubertal rats, suggesting that receptor desensitization may not occur prior to adulthood. Similarly, fluoxetine appears to have different effects on hypothalamic 5-HT_{2A} receptor function in adult and adolescent rats, as shown by the neuroendocrine response to DOI challenge [124].

Two studies have investigated the effects of adolescent SSRI treatment on 5-HT_{1A} receptors in adulthood. These studies report no changes in 5-HT_{1A} receptor binding [125] or function [123] following extended wash-out periods (14–17 days and 14 weeks, respectively). Changes in 5-HT_{1A} binding density do not appear to occur during SSRI treatment of adult animals [126], although decreases in receptor function have been observed [127]. It is currently unknown how 5-HT_{1A} function is affected during treatment in adolescent animals.

In adults, chronic SSRI treatment probably modulates the 5-HT_{2C} receptor in two ways: the receptor becomes desensitized [117] and alterations in pre-mRNA editing modify the balance of different receptor isoforms [128]. The primary transcript of the 5-HT_{2C} receptor is subject to post-transcriptional editing, producing various receptor isoforms that differ in their sensitivity for 5-HT and their ability to activate the receptor's associated G protein, Gαq [129]. Studies have demonstrated that chronic stress alters pre-mRNA editing, and treatment with SSRIs during adulthood reverses these effects [128].

Although the effect of antidepressants on 5-HT_{2C} receptor desensitization in adolescents is unknown, Bhansali *et al.* investigated the impact of 28 days of fluoxetine treatment on adult and adolescent BALB/c mice with or without a history of infant maternal separation (IMS), and reported differential effects of the antidepressant depending on prior stress experiences and age [130]. IMS increased editing, thus reducing the sensitivity of the receptor for 5-HT. In what appears to be a compensatory response for the reduced interaction of the receptor with its G protein, the level of Gαq was also increased in IMS mice. Fluoxetine treatment normalized these effects in adolescents, but only reversed the increase in Gαq in adults. In contrast, normal adolescent mice showed the opposite response to fluoxetine, with increases in pre-mRNA editing without compensatory changes in Gαq binding. This resembles the response to chronic stress [128] and may suggest adverse effects of fluoxetine on the serotonin system in normal adolescent animals. This study provides a strong indication that effects of SSRIs on the developing brain may differ depending on prior history and depressive symptomatology.

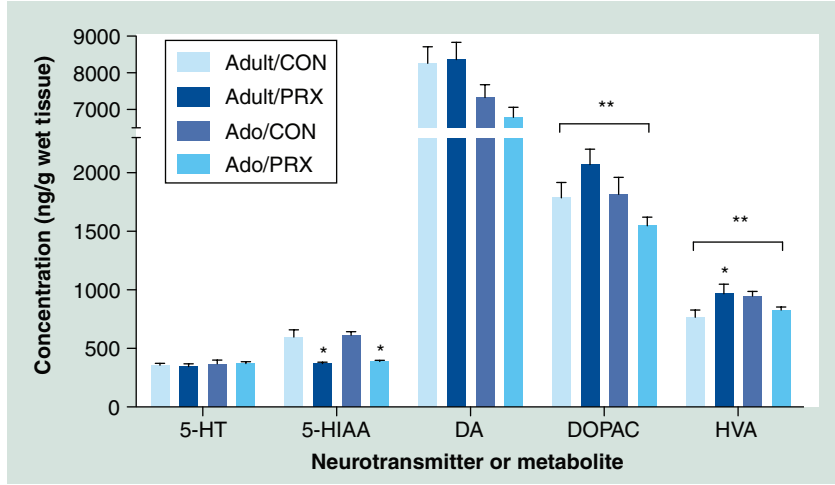

Figure 2. Chronic paroxetine (10 mg/kg in drinking water) exerts differential neurochemical effects in the striatum of adult and adolescent rats (n = 8/group).
*Significant treatment effect compared with age-matched controls ($p < 0.05$).
**Significant age × treatment interaction effect ($p < 0.05$).
5-HIAA: 5-hydroxyindoleacetic acid; 5-HT: Serotonin; Ado: Adolescent; CON: Control; DA: Dopamine; DOPAC: 3,4-dihydroxyphenylacetic acid; HVA: Homovanillic acid; PRX: Paroxetine.
Adapted with permission from [86].

Dopamine system

The mesocorticolimbic dopamine system, originating from the VTA and connecting with the PFC, amygdala, hippocampus and nucleus accumbens, is thought to play a role in the regulation of motivation, hedonic state, reward, social behavior, cognition and emotional control [112]. Given that anhedonia and loss of motivation are two of the core symptoms of depression, it is unsurprising that dopamine has been implicated in depression and the antidepressant response [131,132].

With the exception of high-dose sertraline, SSRIs have low affinity for components of the dopamine system, yet they are capable of influencing dopaminergic function after both chronic and acute administration [133]. Temporary attenuation of mesolimbic dopaminergic activity by acute SSRI treatment, mediated by serotonergic activation of 5-HT_{2C} receptors, is thought to contribute to the early anxiogenic effects and delay in efficacy of the SSRIs [134]. Conversely, chronic SSRI treatment in adults has been associated with increased firing of mesocorticolimbic dopaminergic neurons [135] and increases in synaptic dopamine [136], suggesting that disinhibition of the dopamine system may be important for the therapeutic effects of the SSRIs [137].

Only one study has investigated whether SSRIs have similar effects on the dopamine system in adolescents. Karanges *et al.* conducted a direct adolescent versus adult comparison of the behavioral and neural effects of chronic paroxetine in rats, reporting developmental differences in the effects of the drug on dopamine metabolites and turnover in the striatum (see Figure 2), and dopamine transporter binding density in the nucleus accumbens [86]. Specifically, paroxetine increased measures of dopamine turnover, homovanillic acid (a dopamine metabolite) and dopamine transporter in adult rats, with no such effects in adolescents. As reviewed earlier, the developing brain may not respond to chronic SSRI treatment with desensitization of the 5-HT receptor subtypes involved in the moderation of dopamine release, thus preventing the dopaminergic upregulation commonly seen in adults. These findings potentially explain some of the adverse behavioral effects and lack of therapeutic efficacy reported in adolescents.

Norepinephrine system

Dysfunction of the noradrenergic system has been implicated in depression and anxiety disorders [138], particularly with regard to symptoms associated with arousal, energy and vigilance [139]. Antidepressant drugs such as the TCAs and SNRIs have direct effects on noradrenergic function, while SSRIs appear to affect this system primarily through serotonergic mechanisms [139]. Specifically, chronic treatment with SSRIs in adults has been associated with reductions in extracellular norepinephrine in the amygdala and LC [140] and reductions in spontaneous and sensory-evoked firing of LC neurons [141]. Interestingly, inhibition of LC neuronal activity has been reliably associated with other antidepressant therapies including TCAs, MAOIs and electroconvulsive shock [135,141]. This has been proposed as a mechanism by which antidepressants facilitate dopamine release from the VTA [142], contributing to the relief of depression-related symptoms such as anhedonia.

However, a recent study by West *et al.* (see [87], and its addendum [143]) demonstrates that short-term treatment with some antidepressants may actually produce opposite effects in adolescent rats. In contrast to the decrease in LC neuronal activity found in adults, short-term administration (over 2–4 days) of paroxetine or venlafaxine increased LC activity in adolescents, with reductions emerging after 8 or more days of treatment. Compellingly, the directional changes in LC activity reflected depressive-like behaviors in the forced swim test, suggesting that hyperactivity of LC neurons may contribute to depressogenic effects of antidepressants in some adolescents. Indeed, increases in LC neuronal activity have been previously observed in conjunction with depression-like behaviors in animal models of chronic stress [142].

However, certain components of the norepinephrine system are not commonly modulated by SSRI treatment. With the exception of paroxetine, which is known to block norepinephrine reuptake at high doses [144], SSRIs do not appear to modulate norepinephrine transporter binding or affinity [105] or total tissue norepinephrine [86] in adult or adolescent rodents.

Effects on neurogenesis & synaptic plasticity

The neurotrophic hypothesis of depression and antidepressant action, reviewed extensively elsewhere [145–149], proposes that reductions in hippocampal neurogenesis and/or neurotrophic factors play a role in the etiology of depression, and that antidepressants act to normalize these deficits. Supporting evidence for the role of neurogenesis in depression includes the hippocampal atrophy and reduced concentrations of neurotrophic factors such as brain-derived

neurotrophic factor (BDNF) in individuals with depression [146], and decreases in neurogenesis and BDNF expression in animals exposed to chronic stress [149]. Conversely, stimulation of neurogenesis is a key feature of many antidepressant therapies, including the SSRIs and other antidepressant drugs [150], exercise [151] and electroconvulsive shock [152], and suppression of these neurotrophic actions can prevent the relief of certain depression- or anxiety-like symptoms by such treatments [150,153,154]. Antidepressant treatment in adults has also been associated with upregulation of BDNF and other neurotrophic proteins [147,155,156], downregulation of proapoptotic proteins [155] and stimulation of dendritic arborization and synaptic plasticity [154,157]. Together, these findings suggest that the actions of antidepressants on neurogenesis may be important for their therapeutic effects [148,154].

Although it is not the purpose of this article to critique this hypothesis (see [158] for a recent critique), it is worth noting that not all studies support a causal relationship between stimulation of neurogenesis and antidepressant action. The behavioral effects of antidepressants appear to be neurogenesis independent in certain strains of rodents such as the BALB/cJ mouse [88], and stimulation of hippocampal neurogenesis appears to be required for relief of anxiety-like but not depression-like symptoms in some animal models [154]. These findings and others have led to the proposal that it is the stimulation of neuronal plasticity and associated processes rather than neurogenesis *per se* that underlies the behavioral response to antidepressants [149,154].

Regardless of whether the effect of antidepressants on neurotrophic processes are an epiphenomenon, the ability of antidepressants to affect synaptic plasticity has important implications for the treatment of adolescents, given the elevation of baseline synaptic plasticity and neurogenesis and the malleability of limbic–cortical links during adolescence [28]. The adolescent response to antidepressants has therefore been investigated more heavily with relation to neuroplasticity than any other aspect of the neural response. However, as with the adult literature, the adolescent literature is complicated by differences in prior stressor exposure, strain, drug, dose and variation in the dependent variables investigated.

Several studies have found no effect of antidepressant treatment on measures of hippocampal cell proliferation, differentiation and/or survival in standard-reared adolescent rodents. For example, following treatment with fluoxetine for 25 days, Cowen *et al.* report no differences in dentate gyrus volume, cell proliferation or cell survival in adolescent rats [28]. Similar findings have been reported in mice treated with fluoxetine during the juvenile and early adolescent periods [90,159]. In addition, in contrast to commonly observed effects in adults, adolescent antidepressant treatment does not appear to stimulate expression of neurotrophic factors, and may even disrupt associated signaling pathways [104,160]. However, it should be noted that these studies either lack an adult comparison group [90,104,159] or show none of the commonly observed neurogenic effects of antidepressant treatment in adults [28,160], limiting robust conclusions on developmental differences.

However, two studies have employed direct adult versus adolescent comparisons investigating the effects of chronic fluoxetine on hippocampal neurogenesis. While both studies report differential age effects, they are seemingly contradictory in direction and mediation by sex. Following administration of fluoxetine (5 mg/kg) to rats for 14–18 days, Hodes *et al.* report increased DNA synthesis and cell proliferation in adult male rats, with no such effects in sex-matched adolescents [161]. The pattern differed in females: aside from a trend toward decreased cell survival in fluoxetine-treated adolescents, fluoxetine did not stimulate hippocampal neurogenesis in either age group. In direct contrast, Navailles *et al.* show no effects of chronic fluoxetine (16 or 25 mg/kg) on neurogenesis in adult mice of either sex, while observing increases in some, but not all, measures of neurogenesis in standard-reared adolescents [98]. The reason for these contradictory findings is unclear, but may be related to dose or species differences. Indeed, higher doses, such as those used by Navailles *et al.* [98], may be required to stimulate neurogenesis in adolescent rodents, which are known to metabolize drugs more rapidly than their adult counterparts [12]. Furthermore, granule cell proliferation and maturation follow different time courses in rats and mice, and are of greater functional importance in rats, with suggestions that the rat hippocampus may better model that of the human [162].

Rodent models of chronic stress may provide a more etiologically valid environment in which to examine the effects of antidepressants on neurogenesis. The studies relevant to this article employing such models have demonstrated modulation of adolescent responses to chronic fluoxetine and tianeptine by early life or adolescent stress paradigms [98,159,163]. In the

study conducted by Navailles *et al.* reviewed earlier, IMS abolished the neurogenic responses to fluoxetine observed in standard facility reared adolescents [98]. Similarly, exposure to adolescent social stress removed the stimulatory effects of tianeptine on synaptophysin, a marker of synaptic plasticity [163]. By contrast, fluoxetine increased hippocampal cell proliferation and survival in adolescent mice exposed to social isolation rearing (SIR), with no such effects in standard facility-reared mice [159]. These conflicting findings may again reflect procedural differences: SIR and IMS may have different neural effects [164], influencing antidepressant action and neurogenesis. Furthermore, the inhibitory effects on hippocampal neurogenesis were only reported following the SIR manipulation in these studies.

Several studies have pointed to a relationship between adult hippocampal neurogenesis, hypothalamic–pituitary–adrenal axis activity and glucocorticoids. Glucocorticoids inhibit hippocampal neurogenesis [165] and the release of neurotrophic factors such as BDNF via activation of the glucocorticoid receptor (GR) [166]. Furthermore, antidepressants stimulate neurogenesis by GR-dependent mechanisms [167] and have been associated with reductions in cortisol and adrenocorticotropic hormone concentrations in treatment responders, but not in treatment nonresponders [168]. As such, changes in corticosterone concentrations with treatment may provide an indication of antidepressant efficacy. Studies investigating adolescent responses to SSRIs have uniformly reported no effects on corticosterone or adrenocorticotropic hormone concentrations during or shortly after treatment [124,161]. However, these studies were conducted in 'normal' animals, who are less likely to show alterations in corticosterone with treatment [169].

As previously inferred, the effects of antidepressants are not restricted to neurogenesis or even to the hippocampal region, but extend to related processes such as neuroplasticity, synaptic remodeling and synaptogenesis (**Box 2 & Table 3**). Unsurprisingly, there are indications that antidepressant treatment during adolescence may cause lasting perturbations in normal developmental processes, altering dendritic spine development and synaptic outgrowth. For example, chronic treatment of rats with fluoxetine from P21 until P42 prevented the normal age-related increase in dendritic spine density in the CA1 region of the hippocampus [30]. This contrasts with reports that fluoxetine inhibits stress-induced atrophy of dendritic spines in adults [154], suggesting that hippocampal plasticity may be differentially affected by fluoxetine in adolescents. However, these effects may be specific to dendritic arborization, given indications that hippocampal N-acetyl aspartate, a marker of neuronal density and function, appears to increase in response to SSRI treatment in both adult humans [170] and adolescent rodents [171].

Chronic SSRI treatment during adolescence also seems to moderate synaptic plasticity in the amygdala. The polysialylated form of the neural cell adhesion molecule (PSA-NCAM) is a promoter of neurite and synaptic outgrowth and plays a key role in neuronal development [172]. Generally, upregulation of PSA-NCAM expression is indicative of increased synaptic remodeling, while reductions may indicate regressive structural changes [173]. In adult rodents, fluoxetine increases PSA-NCAM expression in the medial PFC and parts of the hippocampus, but decreases expression in the amygdala [173]. In a recent study, Homberg *et al.* measured lasting changes (14–17 days post-treatment) in PSA-NCAM in adult and adolescent rats treated chronically with fluoxetine [125]. In line with previous findings, fluoxetine tended to reduce PSA-NCAM concentrations in the amygdala of adult rats. By contrast, however, there was a trend towards increased PSA-NCAM expression in the amygdala of adolescent rats, suggesting increased amygdala plasticity in this age group in response to fluoxetine treatment. It is possible that these neuroplastic effects may underlie the increases in behavioral despair observed selectively in adolescent rats in this study.

Pharmacogenetics of adolescent antidepressant response

As mentioned earlier, antidepressant medications appear to be associated with efficacy or alternatively, with adverse effects, in certain subgroups of the adult and adolescent population. It has been hypothesized that genetic variation may play a role in determining treatment response, and pharmacogenetic approaches provide a means whereby such genotype–response associations can be investigated. Literature on the pharmacogenetics of the antidepressant response in adult populations is extensive (see [174–176] for recent reviews). Notable and replicated associations with treatment response include polymorphisms within the *5-HTT*, *BDNF*, *TPH1*, *5-HT*$_{1A}$ and *5-HT*$_{2A}$ receptor subtype and *CYP2D6* genes [176]. In addition, certain genes have been associated with adverse effects, particularly antidepressant-induced mania (e.g., *5-HTT*

Box 2. Hippocampal protein expression is differentially altered by paroxetine in adolescent and adult rats.

- A recent study in our laboratory examined the effects of the selective serotonin-reuptake inhibitor paroxetine on the hippocampal protein expression profile of adolescent (postnatal day 28–49) and adult (postnatal day 70–91) rats via 2D gel electrophoresis proteomics. As in our previous study [86], we administered paroxetine in drinking water at a target dose of 10 mg/kg for 22 days. Of the 30 proteins significantly altered by paroxetine administration, eight were altered only in adolescents and ten only in adults, suggesting differential regulation of expression profiles by paroxetine in adult and adolescent rats. Five such proteins are presented in Table 3.

Data taken from [Karanges E & McGregor IS, Unpublished Data].

polymorphisms) and treatment-emergent suicidal ideation (e.g., *BDNF*, *FKBP5*, *CREB1* and *GRIA3* polymorphisms) [174,177].

However, it is not possible to extend these findings to adolescent populations. Genes and their protein products can have different expression patterns, functions and interactions with other genes at different stages of development, thus associations between genes and treatment response may differ in younger populations. We have identified five pharmacogenetic studies of antidepressant response in children and adolescents (see Table 2), some of which have been reviewed previously [109]. All are of relatively small scale and most are open-label, therefore the findings within must be treated with caution until sufficiently replicated. Furthermore, treatment response is unlikely to be moderated extensively by any one gene, but rather by a combination of many environmental and genetic factors [178]. Regardless, these studies may inform future research by highlighting potential moderators of antidepressant response in pediatric and adolescent populations.

One of the most extensively researched polymorphisms in adult populations is the 5-HTT-linked polymorphic region (*5-HTTLPR*) within the promoter of the *5-HTT* gene (*SLC6A4*). Studies have shown that the short (*s*) form of this variable-length repeat region is less transcriptionally active than the long (*l*) form, and has been associated with increased risk of major depressive disorder and other psychiatric diagnoses [179], poorer antidepressant response [180], and greater propensity to develop adverse effects [176], at least in caucasian populations. Accordingly, this polymorphic region has been investigated in all five known pediatric studies on the pharmacogenetics of antidepressant response. Of these, two report an association between poorer response to citalopram and the *s* allele or *ss* genotype in

Table 3. Hippocampal protein expression changes following chronic paroxetine treatment of adolescent and adult rats.

Protein	Fold change		Protein function	Implications and comments
	Adolescent	*Adult*		
Phosphodiesterase 10A (PDE10A)	↔	↓ 6.48	Responsible for degradation of adenosine and guanine nucleotides; role in regulation of cAMP and cGMP signaling	PDE10A polymorphisms have been associated with major depression [207]
Neurogenin 1	↔	↑ 4.19	Neurotrophic protein	Neurotrophic actions of antidepressant therapies may be important for their therapeutic effects [153]
BH3-interacting domain death agonist (BID)	↑ 4.34	ND	Proapoptotic member of the Bcl-2 family; sequesters antiapoptotic proteins (e.g., Bcl-2) and activates proapoptotic family members (e.g., Bax and Bak)	BID inhibitors have antidepressant properties [208]
PKC	↓ 3.12	↔	Phosphoinositide signaling; phosphorylation of proteins implicated in cell proliferation, cell differentiation, apoptosis and neurotransmitter release	Reductions in PKC signaling linked to adolescent suicide [209]
Syntaxin 7	↑ 5.74	ND	Component of the endosomal SNARE complex; role in the transport of neurotransmitter-containing vesicles	Implications for serotonin neurotransmission

2D gel electrophoresis proteomic analysis was conducted on hippocampal samples (n = 6/group) from adolescent (postnatal day 28–49) and adult (postnatal day 70–91) Wistar rats treated with paroxetine (10 mg/kg in drinking water) or standard drinking water for 22 days. Significant alterations in protein expression are expressed as fold change in comparison with age-matched vehicle-treated gels.
↔: No difference versus controls; ↑: Increase; ↓: Decrease; ND: Not detected.
Data taken from [Karanges E & McGregor IS, Unpublished Data].

children and adolescents with depression or anxiety disorders [181,182]. In addition, the *ss* genotype was associated with higher rates of suicidal ideation, although this was not restricted to treatment-emergent effects [182]. These studies suggest that reduced expression of the 5-HTT may contribute to poor treatment outcome in adolescents, as in adults. However, it should be noted that these two studies used patients from the same population pool, potentially limiting the generalizability of these results. Indeed, the *5-HTT* polymorphism was not associated with treatment response [183,184], suicidal events [183] or antidepressant-induced mania [185] in other pediatric populations. Interestingly, despite finding no association between *5-HTT* polymorphism and treatment response in young patients with depression, Joyce *et al.* report an association between the *ss* genotype and poorer response to fluoxetine in patients older than 25 years [184].

There are also other indications that variations in serotonergic function may influence SSRI response in children and adolescents. TPH2 is the rate-limiting enzyme in 5-HT biosynthesis, and there is some indication that polymorphisms in *TPH2* may play a role in susceptibility to major depression, suicidal behavior and antidepressant response in adult populations, although these associations have not been replicated [176]. Similarly, there is some evidence that the *TPH2* polymorphisms may predict antidepressant response in adolescents, whereby carriers of a *T* allele in the *TPH2* promoter (*G-703T*; *rs4570625*) show a somewhat poorer antidepressant response to citalopram [181]. This study also demonstrates an additive effect of this *TPH2* polymorphism and the *5-HTTLPR s* allele in predicting lower remission rates.

Finally, results from the Treatment of SSRI-Resistant Depression in Adolescents (TORDIA) study point to a relationship between polymorphisms in the *FKBP5* gene and onset of suicidal events during SSRI treatment [183]. The *FKBP5* gene encodes a co-chaperone protein that moderates the sensitivity of the GR to glucocorticoids. Certain polymorphisms in this gene increase the GR-induced expression of *FKBP5*, decreasing the sensitivity of the GR to glucocorticoids and impairing negative-feedback regulation of the hypothalamic–pituitary–adrenal axis in healthy controls, with opposite effects in many clinical populations [186]. In adult populations, these alleles have been associated with major depressive disorder and other psychiatric diagnoses [186], as well as treatment response to antidepressants [187]. However, while Brent *et al.* report associations between the *FKBP5 rs1360780 TT* genotype and suicidal events in the TORDIA population [183], the *T* allele has been associated with better response to antidepressants in adults [187,188], suggesting that these polymorphisms may have differential effects in different age groups.

Conclusion

Despite their status as the current treatment of choice for depressive and anxiety disorders in children and adolescents, many questions remain concerning the efficacy and safety of SSRIs in this population. Given the malleability of the adolescent brain to environmental stimuli, exposure to psychotropic drugs during this developmental period can have unexpected short-term and enduring neural consequences. Indeed, studies in laboratory animals demonstrate a myriad of differences between the adult and adolescent neural response to SSRIs. Most notable are the age-specific alterations in monoaminergic components. Differential effects on the serotonin system (such as regional 5-HTT upregulation and the absence of typical desensitization in serotonergic receptor function) likely underlie differential dopaminergic and noradrenergic responses. Antidepressant administration during adolescence may also modify normal developmental neurotrophic processes, having lasting effects on the maturation of the brain regions involved in emotional regulation. However, the nature of these effects may be moderated by genetic and environmental factors including early life experiences, sex and coexisting psychopathology. In the absence of more certain conclusions on the short-term and enduring behavioral and neural consequences of antidepressant exposure during adolescence, the treatment of young persons with these agents should be approached with caution.

Future perspective

Although developmental stage is an obvious mediator of neural response to antidepressants, the precise nature of these effects and their links to behavioral response is not yet clear. The mechanisms by which antidepressants produce their therapeutic effects are complex and largely unknown, thus further research is required, even in adult populations. Despite this, the current findings on antidepressant effects in adults can guide future research into effects on adolescent populations.

Thus far, there has been a strong focus on monoaminergic and neurotrophic mediators of adolescent response to antidepressants. However,

there is increasing evidence that antidepressant action may be mediated by other systems and processes, many of which mature throughout adolescence. For example, glucocorticoid signaling is a recently recognized contributor to the antidepressant response [166], and it is of particular interest given the susceptibility of the brain to glucocorticoids during adolescence [43]. Epigenetic mechanisms such as histone acetylation, histone deacetylation and DNA methylation have also been associated with chronic stress, depressive disorders and the antidepressant response [189,190]. Indeed, chronic fluoxetine stimulates the expression of methyl-CpG DNA binding domain proteins and histone deacetylase 2, repressing gene expression in GABAergic interneurons of the adult rat brain [191]. Epigenetic mechanisms have also been implicated in synaptic plasticity and the enduring neurobiological consequences of adolescent recreational drug use [192], suggesting a potential role in the antidepressant response in adolescents. Other mechanisms of interest include glutamatergic [193] and GABAergic neurotransmission [194], regulation of proinflammatory cytokines [195] and moderation of serotonergic signaling by miRNAs [196].

Currently, there is a paucity of human research on the neural response of young people to antidepressants, although pharmacogenetic studies are emerging. Ultimately, the goal of pharmacogenetic research is personalized medicine, whereby clinicians tailor treatment to individual patients based on genetic indicators of a favorable response. Progress toward this goal, whether in pediatric or adult populations, requires replication of previous findings with adequately powered and well-controlled studies [109,175].

Executive summary

Adolescent neural development

- The developing brain is a highly malleable structure that is susceptible to environmental influences.
- Exposure to psychotropic drugs during the adolescent period can have lasting consequences on brain development, as well as having unexpected behavioral and neural outcomes in the short term.
- Adolescent brain development is characterized by synaptic regression and pruning, increases in myelination, strengthening of connections between limbic and cortical regions and maturation of monoaminergic systems.

Antidepressant treatment of children & adolescents

- Selective serotonin-reuptake inhibitors (SSRIs) are the first-line pharmacological treatment for adolescent depressive disorders.
- SSRIs, with the exception of fluoxetine, have minimal efficacy in children and adolescents.
- Reports that SSRIs are associated with an increased risk of psychiatric adverse effects such as suicidal ideation in children and adolescent populations have led the US FDA to introduce a black box warning on all SSRIs.
- The mechanisms underlying SSRI-induced suicidality are unknown.

Neural effects of antidepressants in adolescents: considerations in reviewing the literature

- Most of the available knowledge on neural effects of antidepressants in adolescents comes from animal studies.
- Experiments using 'normal' animals are valuable in disentangling antidepressant response from disease state and in examining likely effects in nondepressed clinical populations, but are unable to demonstrate corrective effects of the drug on aberrant states or drug–disease interactions.
- Conclusions may differ depending on drug selection and the timing of drug administration and outcome assessment.

Neural effects of antidepressants on major neurotransmitter systems in adolescent animals

- SSRIs have contrasting effects on serotonin transporter expression and serotonin receptor subtypes in adolescent compared with adult animals.
- Dopaminergic upregulation in response to chronic SSRI treatment may be absent in adolescents.
- Early increases in noradrenergic activity may underlie the adverse psychiatric effects of antidepressant administration in adolescents.

Neural effects of antidepressants on neural plasticity & neurogenesis in adolescent animals

- Antidepressants may have differing effects on neurogenesis depending on rearing environment, dose and species/strain in both adult and adolescent animals.
- SSRIs may interact with increases in neuroplasticity during adolescence, modulating the growth and development of limbic regions.

Human findings: pharmacogenetics of adolescent antidepressant response

- Pharmacogenetic studies of antidepressant response in children and adolescents are rare, small in scale and often open-label; therefore, replication of findings is vital.
- Antidepressant response and/or adverse effects in adolescents have been associated with polymorphisms in the *5-HTT*, *TPH2* and *FKBP5* genes.

Future perspective

- Antidepressants are known to affect a variety of neural systems and processes: future research should consider other hypotheses of antidepressant action. Imaging studies in children and adolescents may reveal important neural correlates of treatment.

Recent brain imaging studies have revealed neural correlates of adolescent psychopathology (e.g., [200]), but few have investigated correlates of antidepressant response in this population (but see [198,199]). Imaging studies have revealed regional effects of antidepressants on brain volume, neuronal activation and biochemistry in adults [200], highlighting the need for corresponding studies in adolescents.

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