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Adolescent Neurodevelopment and Vulnerability to Psychosis

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Abstract

Adolescence is characterized by significant changes in several domains, including brain structure and function, puberty, and social and environmental factors. Some of these changes serve to increase the likelihood of psychosis onset during this period, while others may buffer this risk. This review characterizes our current knowledge regarding the unique aspects of adolescence that may serve as risk factors for schizophrenia spectrum disorders. In addition, we provide potential future directions for research into adolescent specific developmental mechanisms that impart vulnerability to psychosis as well as the possibility of interventions that capitalize on adolescents' unique characteristics. Specifically, we explore the ways in which grey and white matter develop throughout adolescence in typically developing youth as well as those with psychosis spectrum disorders. We also discuss current views on the function that social support and demands, as well as role expectations, play in risk for psychosis. We further highlight the importance of considering biological factors such as puberty and hormonal changes as areas of unique vulnerability for adolescents. Finally, we discuss cannabis use as a factor that may have a unique impact during adolescent neurodevelopment, and subsequently potentially impact psychosis onset. Throughout, we include discussion of resilience factors that may provide unique opportunities for intervention during this dynamic life stage.

Keywords

psychosis; schizophrenia; adolescence; development; social function; cannabis

Introduction

Adolescence is a period of rapid development in brain structure and function (1–3), which supports the transition to the varied demands of adult life. Special opportunities for growth,

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particularly in areas such as social function, also characterize this time (4, 5). However, adolescence also is associated with a vulnerability to psychopathology, whether it be depression, anxiety, or, the subject of this review, psychosis (6, 7). While the prenatal period represents the first window of vulnerability for increasing risk of psychosis, in which early life insults act as diathesis factors in the later development of psychosis (8), the adolescent stage represents a second risk period rife with stressors more proximal to symptom onset (9).

While peak onset of schizophrenia falls between ages 15–25 (10), the incidence of schizophrenia shows an increase beginning around age 14 (6), with approximately 39% of male and 23% of female patients developing schizophrenia before age 19 (11). Furthermore, epidemiologic studies indicate that prevalence of subthreshold psychotic symptoms during late childhood and adolescence is higher than in adulthood (12). Thus, across a spectrum of symptom severity, adolescence is a significant period for emergence of psychosis (for recent review, see (13)). However, despite epidemiological data showing that adolescent-onset psychosis is not an anomaly, but rather reflects the course of illness in a substantial subset of patients, there is a general perception that psychosis in those below age 18 is markedly different from the expected illness trajectory (14, 15). As a result, while there is growing research on developmental factors in the prodromal phase, there is limited research on developmental factors in individuals diagnosed with psychotic disorders. This is important, as intervention within the first two years of onset of fully psychotic symptoms is associated with better functional outcome and maintenance of symptom remission (16), underscoring the critical need to characterize developmental mechanisms early in the course of illness in order to optimize interventions.

Although schizophrenia is often described as a putatively developmental disorder and relationships have been hypothesized between neurodevelopment and psychosis onset (17), the precise nature of any etiological links is still under investigation. Earlier age of onset, as in adolescent-onset psychosis, has been associated with lower premorbid function(18), more hospitalizations(19), poorer cognitive function(20), and poor prognosis(21). Thus, psychosis during adolescence may confer special risk. However, it is also possible that in addition to vulnerability, the neurodevelopmental changes and unique adolescent environment may confer special opportunities for interventions that could be uniquely effective during this dynamic period. This review examines adolescent development, both as it typically occurs and as it may be altered in adolescents with psychosis and those identified to be at clinical high risk (CHR) for psychotic disorders. We discuss several examples of biological and social risk factors that uniquely or disproportionately affect adolescents, as well as the importance of early intervention in psychosis (Table 1; Figure 1). While we discuss adolescence as a unitary construct, in part reflecting the state of available research, it represents a dynamic period, and further study of stages of development within adolescence is merited. Additionally, labels of “psychosis” and “CHR” reflect a spectrum of psychotic symptomatology that spans from increased risk through diagnosis of psychosis (for recent review, see (13)).

Brain Development

Grey Matter Development and Psychosis—During adolescence, although brain volume remains relatively stable (22), grey (GM) and white matter (WM) undergo substantial microstructural changes. GM changes during adolescence (e.g. changes in cortical thickness) are considered to be due to reductions in synaptic density via pruning. Synaptic pruning is facilitated by microglia, which are extremely active in synaptic maintenance and refine circuitry in an activity-dependent manner(23). Synaptic density peaks in early life and shows age-related decreases (24), with developmental trajectories varying by brain region. Lateral frontal, parietal, and occipital cortical regions show an initial increase in cortical thickness in childhood with a peak around age 10, followed by a period of decline in adolescence and stabilization in adulthood (2). Prefrontal pruning is believed to be ongoing into the third decade of life (25), with synaptic density changes associated with age-related improvements in cognitive ability (26). Puberty coincides with a rapid decrease in synaptic density, which is believed to underlie age-related decreases in GM (27). Adolescence is a key period for prefrontal pruning in particular, along with changes in glutamatergic and GABA-ergic neurotransmitter systems (28). Notably, these late-maturing regions support higher level cognitive functions which both continue to mature across adolescence and are impacted in psychosis. In adolescence, stressors (e.g. social stress, cannabis use) that affect microglial functioning may have ramifications for appropriate development of neural circuits and excitatory-inhibitory balance in the brain.

Disruptions in normal developmental pruning processes have long been implicated in the pathogenesis of schizophrenia (29). Documented reductions in cortical GM in schizophrenia are hypothesized to be due to either early (e.g. reduced synaptogenesis early in life) or late (e.g. exaggerated pruning in adolescence) developmental insults (30), or a combination of both. GM differences have even been documented in CHR youth, with progressive reduction in GM associated with transition to psychosis, consistent with an accelerated pruning model (31). In adult patients, cortical GM volume reductions relative to controls have been demonstrated(32) along with decreased density of dendritic spines (33). Recent research in adult schizophrenia samples has validated postmortem findings of lower levels of presynaptic protein markers such as SV2A (34), putatively reflecting an overall lack of synaptic terminals due to excessive pruning. However, evidence suggests that GM decreases are not unilateral across the brain, with region-specific differences in increased versus decreased volume (35). Additionally, GM reductions may be characteristic of a subtype of psychotic illness (36). However, much evidence is from MRI and thus necessarily inferential, and evidence in adolescent samples is severely limited.

Both atypical and typical antipsychotics have been associated with brain volume change over time (37). Though antipsychotics have been associated with GM decreases, medication-naïve samples have also shown this pattern (38), and findings on the impact of antipsychotics on synaptic density are mixed. The potential interaction of antipsychotics and development has spurred discussion on appropriateness of antipsychotic use in pediatric populations and whether antipsychotics impact brain development. Recently, there has been a growing interest in synaptic pruning as a potential treatment target (39), which exemplifies

how the dynamic adolescent period might be leveraged to develop age-targeted treatment strategies.

In addition to synaptic pruning, differences in gyrification have been documented in adolescent schizophrenia patients (40). One theory posits that tension produced by neural connections plays a key role in cortical folding (41), suggesting that pruning-induced alterations in structural connectivity particularly during adolescence would impact gyrification. Though we focus on pruning here, we acknowledge the complexity of GM changes in psychosis. Future reviews may provide key synthesis of extant literature, inclusive of multiple GM developmental processes.

White Matter Development and Psychosis—Myelination of white matter tracts begins in-utero(42) and increases through the second and third decades of life, as assayed by postmortem (42) and imaging studies (3). Recent studies using diffusion imaging techniques have found that WM fractional anisotropy (FA; a putative metric of WM integrity) and mean diffusivity (MD) peak in the majority of regions by age 35 (3), or earlier (43, 44), although many of these regions reach near-mature levels in adolescence, with myelination slowing as adulthood approaches (3). Adolescent WM maturation has been linked to pubertal stage and hormone levels (45). Myelination of WM tracts occurs in a caudal-cranial, posterior-anterior arc (46) such that long-range association tracts and frontaltemporal tracts, which are associated with higher order cognition (43), are undergoing development during adolescence. Importantly, these regions also undergo relatively later pruning processes (as discussed above). While there is preclinical support for FA as an index of myelination (47), some imaging metrics capture additional adolescent changes in WM structure, such as changes in axon diameter (48) and neurite density (49), that have received less attention. Experience-driven changes in WM, including altered oligodendrocyte function and myelination following social deprivation (50), new myelination and remodeling of existing myelin with sensory stimulation (51), and FA increases following motor learning (52), are likely to be important during adolescence, as changes in social and role functions as well as hormonal changes and biological maturation (reviewed below) expose adolescents to a variety of formative new experiences. Finally, GM and WM changes are not fully independent; increases in neural activity may foster increases in myelination (53, 54), however, the relevance of these interactions to psychosis is not well understood.

Psychotic spectrum disorders are commonly regarded as disorders of dysconnectivity, with reductions in FA across nearly all major tracts (54, 55). Although some evidence suggests post-conversion adulthood decline in WM FA among schizophrenia patients (56), reduced FA in long-range association tracts (e.g., inferior longitudinal fasciculus, superior longitudinal fasciculus, inferior fronto-occipital fasciculus) is evident in adolescents with psychosis (57–59), CHR individuals (60, 61), and adolescents with psychotic-like experiences (PLEs) (62, 63). Evidence from cross-sectional and longitudinal studies across the spectrum have suggested these deficits are due to blunting of expected age-related increases in WM volume and FA (59, 64) (see (65) for critical review of these findings related to early vulnerability and developmental models of psychosis). Further research is needed to elucidate the nuanced causal relationship between WM development in adolescence and psychotic symptoms, including how altered WM development relates to

other vulnerabilities, like cognitive (43) and social (66) deficits. Given these changes, myelination is another potential target for age-related treatments (54). One area of interest has been administration of fatty acids, as omega-3 polyunsaturated fatty acids are critical for myelin formation (67); studies have shown mixed effects (68), potentially because it is important to intervene during times of active myelination, such as adolescence.

Functional Connectivity and Psychosis—Similar to structural connectivity, functional connectivity undergoes significant development and reorganization during adolescence (e.g., (69, 70)), yet less work has focused on functional connectivity development in adolescent psychosis (71). Extant studies have found that adolescents endorsing PLEs show functional connectivity alterations similar to adult psychosis patients (72, 73), and that age-related connectivity changes are altered in CHR and PLE-endorsing adolescents in amygdalar (73, 74) and working memory circuits (75). Additional work, including findings from large developmental datasets and adolescent psychosis samples, is needed.

Adolescence as a Window for Intervention—The considerable changes in brain, body, and environment during adolescence suggest a period of greater plasticity relative to adults later in the course of illness, which may be leveraged for unique opportunities to intervene. Decades of research emphasizing early intervention (16) are consistent with the notion of adolescence as a particularly optimal time for intervention.

For example, reducing duration of untreated psychosis (DUP) via early intervention has been consistently associated with greater treatment response, functional improvement, and stable treatment gains (76, 77). It has been proposed that early intervention may limit neurotoxic effects of dopaminergic hyperactivity; however, evidence to support this as the primary mechanism by which DUP contributes to poor outcomes is mixed (78). Given the average age of onset, the optimal DUP during which intervention is most likely to be effective coincides with the adolescent developmental period. Early intervention may be bolstered by or utilize the developmental plasticity of adolescence. In particular, adolescent-focused intervention potentially provides the opportunity to alter the developmental illness trajectory. Despite a compelling theoretical basis (79), empirical data on developmental interventions for psychosis in humans are limited. However, animal studies have provided evidence for the efficacy of developmentally sensitive intervention, with adolescent-focused interventions in animal models of schizophrenia leading to long-term, stable gains maintained in adulthood (80, 81).

Factors Particularly Relevant during Adolescence

Social and Familial Environment—Adolescence is an intense period of social change as adolescents navigate individuation and increasing autonomy. Familial relationships take a less central – and more contentious – social role (82, 83) in favor of peer and romantic relationships (84) that become increasingly hierarchical and complex particularly through early adolescence (83). Peer relationships similarly become more influential in adolescence, with greater impact on mood (85), decision-making (86), risk-taking (4), and substance use (87). Adolescents also show increased neuroendocrine and cardiovascular reactivity

to social stressors relative to children (88) and increased subcortical activation following social rejection compared to adults (89), suggesting special vulnerability to social stress. Chronic social stress begets feelings of loneliness, which peak in adolescence, as incidence of psychotic disorders increases (90).

Individuals who develop psychosis have been shown to have poorer premorbid social functioning in childhood and adolescence(91), and poor social functioning and reduced friend networks are associated with worsening functioning and increased risk of conversion among CHR youth (92, 93). Conversely, PLEs and WM abnormalities among children and adolescents also predict poor social functioning and social competence, respectively (94). Acute social stressors, including peer victimization, during adolescence are associated with increased PLEs in adulthood (95), and CHR youth report higher physical and psychological bullying (96).

Preclinical experiments suggest possible biological mechanisms, including altered dopamine signaling following social defeat (97) and altered oligodendrocyte maturation and myelination in PFC following juvenile social isolation (50). These provide tentative explanations for the associations between WM abnormalities in late-developing regions and social functioning in subsyndromal and prodromal adolescents (66, 94), although this has yet to be thoroughly tested in humans. Additionally, diathesis-stress models suggest that genetic and early life insults increase adolescent vulnerability to stress (8), so tests of interactions between diathesis factors and adolescent stressors on neurodevelopment or psychosis emergence are an important future direction.

Though social changes in adolescence may confer risk, the social context of the adolescent, and specifically the family context, may provide unique opportunity to scaffold treatment that may not be possible once individuals live independently. Existing family interventions for psychosis focus on reducing expressed emotion (EE), the hostile family environment that can emerge when a family member is diagnosed with severe mental illness. Family-focused interventions targeting EE can improve the relationship between caregivers and CHR youth, have prophylactic efficacy, and reduce relapse in fully psychotic youth (98). Beyond EE interventions, adolescent-specific modifications of psychosocial treatments for psychosis are limited. However, interventions for other severe mental illnesses provide compelling evidence that the family environment can be uniquely leveraged during treatment. Interpersonal and Social Rhythm Therapy (IPSRT), an evidence-based psychotherapy for the treatment of bipolar disorder, focuses on the relationship between mood and stressors, regulating sleep-wake and social rhythms, and identifying precipitants to worsening mood(99). In the adolescent modification (IPSRT-A), parents are flexibly involved throughout treatment and reinforce the adolescent's successful use of treatment strategies (100). Though IPSRT-A is indicated for bipolar disorder, benefits of family support in implementation of therapeutic strategies at home may generalize to psychosis interventions and may help improve treatment adherence.

Role Changes—In addition to social changes, adolescents are tasked with navigating role changes, especially increasing academic and work demands. Across cultures, the transition to "adulthood" is marked by full assumption of adult roles and responsibilities (101).

Despite this, the research base that focuses on how role changes affect typically developing adolescents' mood and later functioning is much smaller than that on social change, often focusing on early adulthood and large role changes such as graduation or entering the workforce (102). Role responsibilities and transitions, especially in academics, are commonly cited as the most significant stressors for adolescents (103). However, moderating this stress is important, as academic functioning and educational attainment (primarily associated with adolescence) have been found to correlate with higher levels of life satisfaction and health even decades after this life stage ends (104). Research investigating the predictive power of role changes for later psychopathology and symptom severity is more limited than for social functioning. Findings around role changes and psychopathology are mixed, potentially due to inconsistencies in measurement (105). However, academic performance has been a research target for understanding the relationship between role functioning and adolescent psychosis (106). Findings are mixed (106), but suggest that premorbid academic performance differs among psychosis patients, first-degree relatives, and healthy controls (107). More broadly, role functioning in CHR youth appears to be predicted by WM abnormalities (66), and to in turn predict severity of psychosis symptomatology (108). Additionally, stressors, such as role changes, are believed to contribute to the emergence or worsening of psychotic symptoms (109). Stress exposure leads to cortisol release which is related acutely to dopamine release (110) and chronically with potential neurotoxic effects, particularly on hippocampal morphology (reviewed in (111)).

Pubertal Risk Factors—One definition of the onset of adolescence is with puberty (112), which begins with adrenarche, the release of androgens from the adrenal gland (113, 114). Androgen levels reach adult levels in the late teens or early 20's (115) and are associated with secondary sex characteristic development (114). Gonadarche is the activation of the hypothalamic-pituitary-gonadal (HPG) axis (114), which stimulate ovaries and testes to produce estrogen and testosterone, ultimately resulting in sexual maturity. However, while hormones may seem attractive as a measure of the timing of adolescence, the issue is complex, as such measures relate to, but do not perfectly mirror, physical development (112). Moreover, hormone measures vary widely, both within and between pubertal stages (116). Thus, multimodal assessments are critical for accurate assessment. In addition to impacting the body, hormonal changes during puberty may profoundly affect neurodevelopment (114). Effects can include organizational effects (structural changes) and activational effects (fluctuating activity) (117). During typical adolescent development, dramatic increases in hormones (114), such as testosterone and estradiol (118), contribute to initiation of a period of structural reorganization involving GM volume decreases and increases in WM volume and integrity (45), consistent with cortical pruning and myelination. Moreover, such hormonal changes in have been associated with cognitive functions developing during adolescence such as affective reactivity and reward processing (118, 119). In addition to gonadal hormones, stress hormones such as cortisol also increase in basal levels during puberty (120), as does cortisol release in response to stress (121). The neurological effects of stress and cortisol exposure in adolescence also seem to be longer-lasting and more pervasive compared to adulthood (122).

Support for a role of hormones in psychosis comes from longstanding findings of a difference in incidence and onset in males and females (6, 123), as well as altered hormone levels in adult patients (124, 125). One hypothesis is that estrogen may be neuroprotective (126, 127), potentially through buffering the loss of excitatory synapses (128), and influence on dendritic spine density (129). In addition to potential estrogen effects, there is also growing evidence for reduced testosterone in adults with schizophrenia(123). Given overlap between the post-pubertal period and psychosis, there is also interest in age-specific impacts of hormonal changes in adolescence, both in terms of risk and protective factors. For example, sex hormones may be particularly relevant to brain-behavior relationships, as activational effects may increase sensitivity of neural circuits to environmental input (114). In addition, elevated dopaminergic signaling during adolescence may be moderated by testosterone (130), which also predicts structural connectivity of thalamo-striato-cortical networks (131) that have been implicated in schizophrenia and CHR youth. Recent work has investigated potential hormonally-based interventions, but not in adolescent patients (123). In addition to gonadal hormones, the role of HPA axis function and development in psychosis onset has garnered significant study (e.g., (111, 132, 133)), and there is evidence for coupling of HPA and HPG axes (134). Increased basal cortisol and blunted cortisol reactivity have been found in psychosis populations (reviewed in (133)). While theoretical links have been drawn between hormonal changes, brain maturation, and psychosis onset (135, 136), empirical data are scarce and further research is needed (125). Further investigation of how hormonal changes, broadly construed, intersect or interact with early stages of psychosis will be critical for our understanding of divergent developmental trajectories (137, 138).

Adolescent Cannabis Use—Substance use, particularly alcohol and cannabis, is often initiated in adolescence (139). Though alcohol has been associated with increased psychosis risk, the neurodevelopmental mechanisms are unknown (140). For the purposes of this review, we focus on cannabis given the depth of literature focused on neurodevelopmental impacts of cannabis. Furthermore, cannabis use has become of particular interest as access to cannabis has changed with legalization of medical and recreational cannabis use in several states in the US. Additionally, cannabis use may have distinct neural effects in adolescence.

Cannabis acts on the brain's endocannabinoid system, which, in part, plays a key role in PFC maturation. Tetrahydrocannabinol (THC), the main psychoactive component of cannabis, is associated with cannabinoid receptor type 1 (CB1) downregulation on neurons and cannabinoid receptor type 2 (CB2) upregulation on microglia (141). CB1 mediates developmental processes, including the GABA-ergic PFC neuron maturation believed to support development of inhibitory control (142). Appropriate development of the GABA system is key to excitatory/inhibitory balance, with disruptions leading to PFC dysfunction (143). GABAergic dysfunction and prefrontal hypofunction are indicated in psychosis pathophysiology, and the impact of cannabis use on pruning and the GABA system may exacerbate risk for or contribute to psychotic onset (143). Given the role of microglia in pruning, adolescent THC exposure in rodents potentially alters the neurodevelopmental trajectory (142), with microglia alterations and related cognitive deficits persisting into adulthood (141). Alternatively, a recent meta-analysis of human studies suggests cannabis

use has a small effect on cognitive functioning in adulthood, which is reduced by discontinuing use (144). While existing literature provides a compelling rationale for adverse effects of adolescent cannabis use, intensity and longevity of its effects remains an empirical question.

Despite growing evidence for psychogenic properties of THC, the relationship between adolescent cannabis use and psychosis risk is not straightforward, namely due to the differential effects of THC compared to other cannabinoids, such as cannabidiol (CBD) (Figure 2). CBD acts as an antagonist for CB1 and CB2 receptors and may have opposite neural effects as THC, and thus may not have the same psychosis-inducing or risk-heightening effects (145, 146). CBD can potentially alleviate psychotic symptoms and may act as a D2 antagonist, in a way that is analogous to atypical antipsychotics (147). Peripubertal CBD exposure prevents onset of psychosis-like behaviors in a rodent model of psychosis risk (148).

Evidence suggests that cannabis can impact specific brain developmental processes in adolescence, indicating a sensitive period for adverse effects of cannabis use on psychosis risk particularly in light of differential effects in adults versus adolescents. Adolescent cannabis use may also interact with genetic risk for psychosis (149). However, the relationship between adolescent cannabis use and psychosis risk is complex, and the impact of potentially opposing effects of THC and CBD, along with environmental, genetic, and behavioral moderators requires further study.

Conclusions

A greater understanding of the opportunity and challenges that accompany adolescence has driven a push to carve out adolescent medicine, and adolescent mental health, as unique focus areas (150). Work focusing on adolescence has potential to not only reveal truths about the etiology of complex illnesses that arise during this period, but also to identify aspects of the adolescent experience that can be leveraged to improve outcomes. We have endeavored here to focus on neural changes, social and role changes, onset of adrenarche and gonadarche, and increased use of cannabis that construct a unique window of vulnerability in which the adolescent is highly susceptible to the onset of psychosis. We also have endeavored to highlight further research questions, including evaluation of the effects of many other risk factors that exist for adolescents (e.g., trauma), continued research into diathesis factors and interaction with stressors that contribute to heightened vulnerability, and investigation into factors that may moderate the effects of these stressors on the development and severity of symptoms (e.g. early intervention, medication). Moreover, adolescence is not a unitary period, and it is likely that all of these risk and protective factors fluctuate and interact across this age range. Gaining a finer understanding of the relative timing of brain development, hormonal changes, risk factors, and symptoms, is going to be critical for identifying age appropriate or age targeted intervention points. In addition, research that not only identifies developmentally specific treatment targets, but that takes advantage of the unique strengths of the adolescent social and family environment to maximize existing treatments, may be able to make strides towards improving some of the struggles faced by these youth.

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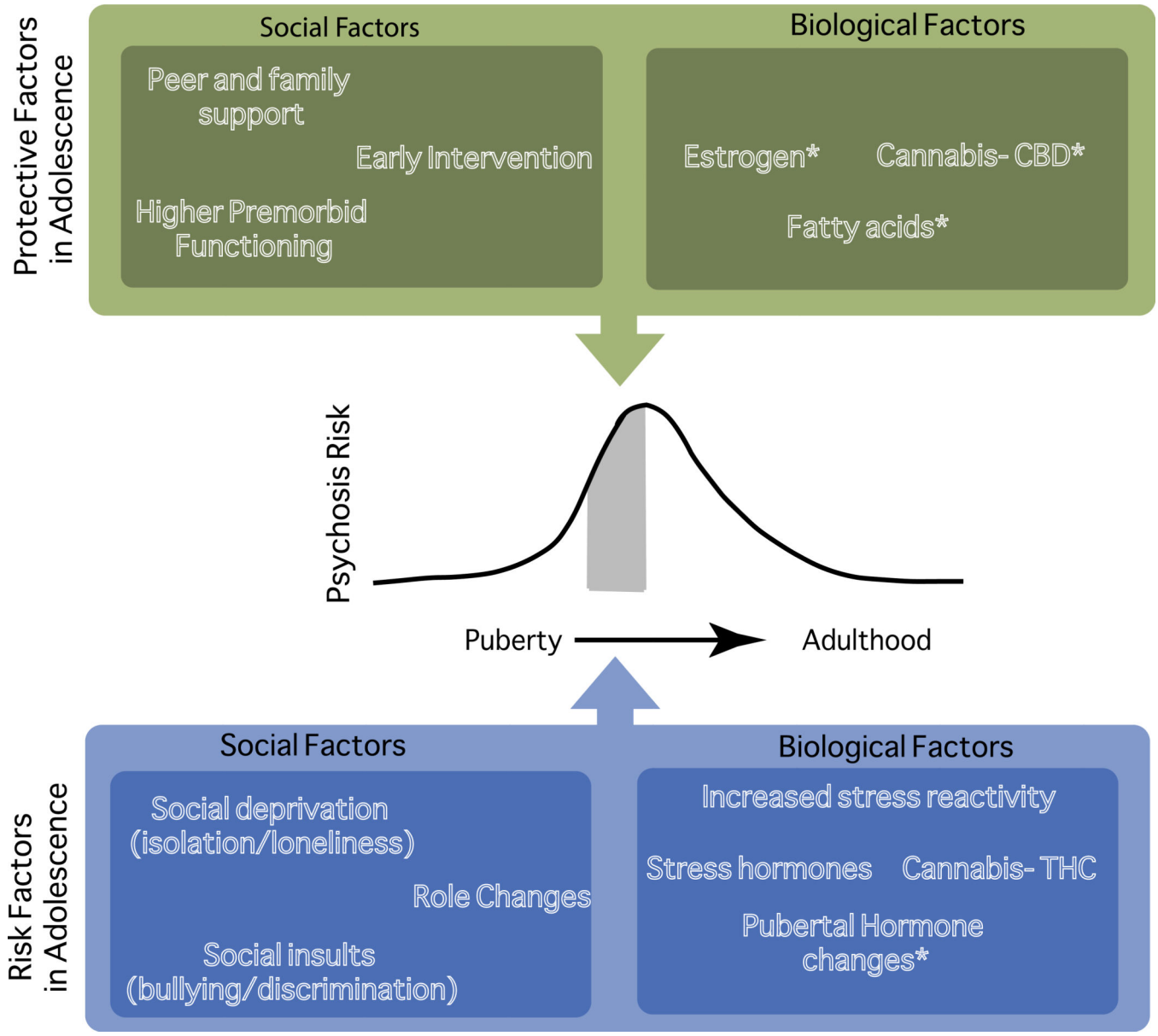

Figure 1.
Protective factors, risk factors, and psychosis risk in adolescence. CBD, cannabidiol; THC, tetrahydrocannabinol. *Areas of limited research support.

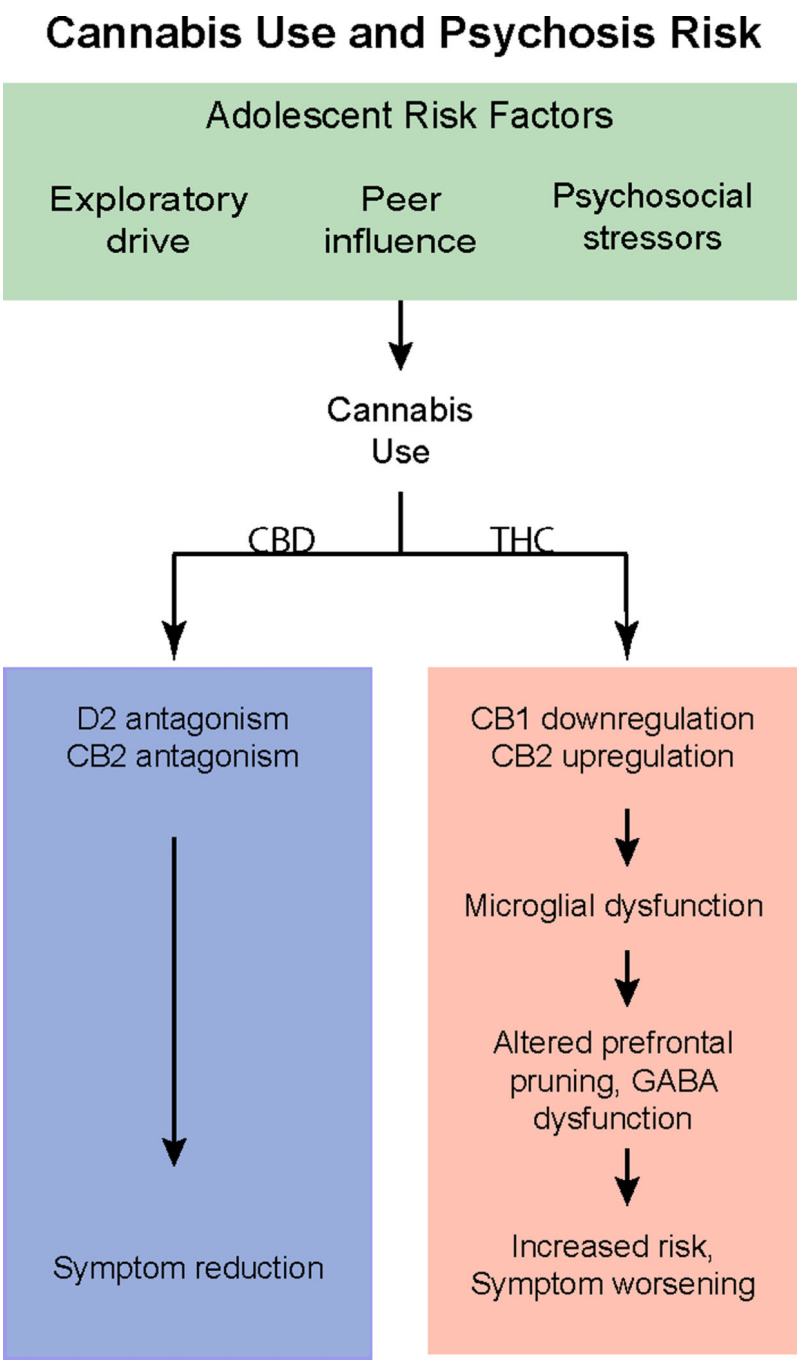

Figure 2.

Cannabis use and psychosis risk in adolescence. CB1, CB_1, receptor; CB2, CB_2 receptor; CBD, cannabidiol; GABA, gamma-aminobutync acid; THC, tetrahydrocannabinol.

Table 1.

Biological and Psychosocial Factors That May Contribute to Psychosis Risk in Adolescence

Example Risk/ Resilience Factors	Potential Mechanism(s) in Adolescence	Impact on Psychosis Risk	Areas for Future Study
Biological Factors			
Accelerated Pruning	Alters cortical thickness, particularly in prefrontal regions believed to support development of higher order cognitive function, which in turn may contribute to cognitive deficits Disrupts excitatory–inhibitory balance in brain via impact on glutamatergic neuron functioning	↑	Validation of presynaptic protein marker findings in adolescent psychosis samples Identification of moderators of GM decreases Evaluation of interaction of antipsychotic medication use and GM developmental processes
Blunted Myelination	Alters maturation of long-range tracts associated with higher order cognitive function	↑	Evaluation of efficacy of WM treatments such as fatty acid administration during the adolescent developmental period Characterization of relationship between structural and functional connectivity specifically in adolescent psychosis samples
Pubertal Sex Hormones	Testosterone[a] Affects organizational and activational processes in the brain, which may make the brain more sensitive to environmental input Moderates dopaminergic signaling, associated with changes in thalamo-cortico-striatal networks	–	Validation of accurate puberty measures and evaluation of hormone effects using multimodal measures Investigation of hormonal correlates in adolescent psychosis samples Evaluation of interaction of HPG and HPA axes
	Estrogen[a] Buffers loss of excitatory synapses and changes in dendritic spine density	↓	
Cannabis Use: THC	Promotes downregulation of CB_1 receptors on neurons, which alters maturation of PFC GABAergic neurons Promotes upregulation of CB_2 receptors on microglia, which alters synaptic pruning	↑	Continued investigation of the longevity and intensity of THC-induced brain alteration Evaluation of moderators of THC-related brain change, including age at first use and frequency of use
Cannabis Use: CBD	Acts as antagonist for CB_1 and CB_2 receptors[a] Acts as a D_2 antagonist, similar to atypical antipsychotic medications[a]	–	Evaluation of mixed THC/CBD use Investigation of longevity and intensity of CBD-related symptom relief and brain change
Psychosocial Factors			
Prophylactic Intervention in At-Risk Individuals	Reduces potential neurotoxicity due to dopaminergic hypersensitivity[a] Decreases oxidative stress, which in turn may limit reductions in PFC interneuron activity[a] Decreases stress responsivity/anxiety response, which in turn may reduce hippocampal damage believed to partially drive dopamine dysfunction[a]	↓	Validation of animal models of psychosis risk states Continued research on biological changes associated with early intervention in humans Mapping of interventions onto biological mechanisms in human studies

Example Risk/ Resilience Factors	Potential Mechanism(s) in Adolescence	Impact on Psychosis Risk	Areas for Future Study
Social Stressors (e.g., Defeat, Isolation)	Alters dopamine signaling following defeat Alters oligodendrocyte maturation, subsequently alters myelination in prefrontal regions following isolation	↑	Evaluation of interaction of diathesis and adolescent stressors on psychosis emergence Exploration of mechanisms linking social functioning and neural change (e.g., myelination) in humans
Role Stressors (e.g., Increased Academic Demands)	Alters cortisol release, which in turn modulates dopamine response Changes hippocampal morphology due to cortisol response	↑	Identification of developmental effects of stress in adolescent psychosis samples

CBD, cannabidiol; GABA, gamma-aminobutyric acid; GM, gray matter; HPA, hypothalamic-pituitary-adrenal; HPG, hypothalamic-pituitary-gonadal; PFC, prefrontal cortex; THC, tetrahydrocannabinol; WM, white matter.

[a] Areas of limited research support.