

Puberty Initiates Cascading Relationships Between Neurodevelopmental, Social, and Internalizing Processes Across Adolescence

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ABSTRACT

Adolescence is a period of dramatic developmental transitions—from puberty-related changes in hormones, bodies, and brains to an increasingly complex social world. The concurrent increase in the onset of many mental disorders has prompted the search for key developmental processes that drive changes in risk for psychopathology during this period of life. Hormonal surges and consequent physical maturation linked to pubertal development in adolescence are thought to affect multiple aspects of brain development, social cognition, and peer relations, each of which have also demonstrated associations with risk for mood and anxiety disorders. These puberty-related effects may combine with other nonpubertal influences on brain maturation to transform adolescents' social perception and experiences, which in turn continue to shape both mental health and brain development through transactional processes. In this review, we focus on pubertal, neural, and social changes across the duration of adolescence that are known or thought to be related to adolescent-emergent disorders, specifically depression, anxiety, and deliberate self-harm (nonsuicidal self-injury). We propose a theoretical model in which social processes (both social cognition and peer relations) are critical to understanding the way in which pubertal development drives neural and psychological changes that produce potential mental health vulnerabilities, particularly (but not exclusively) in adolescent girls.

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Adolescence is a period of significant vulnerability to the emergence of mental health disorders (1). In particular, it is a critical window for the emergence of internalizing (i.e., mood and anxiety) disorders, especially in girls (2,3). Many theories have been advanced to account for how, when, why, and for whom internalizing symptoms and disorders emerge in adolescence, which spans roughly the second decade and half of the third decade of life. Collectively, these approaches consider a wide range of biological, cognitive, and affective aspects of relevant developmental processes including puberty, brain development, cognitive style, emotional reactivity, and psychosocial stress, and the fundamental role of social factors has often been highlighted (4–6).

Despite these important theoretical insights, there has been a tendency to examine risk factors independently from each other, despite the acknowledgment that multiple processes operate together to exert deleterious effects on adolescent development. To that end, there is great promise in taking a multilevel and integrative approach, whereby epidemiological and etiological insights combine to identify modifiable risk factors (7,8). This review focuses on adolescent-emergent internalizing disorders, specifically depression, anxiety, and nonsuicidal self-injury. We first summarize sex disparities and recent cohort effects in these disorders, which leads to a consideration of the potential prominent role of puberty, a 5- to 7-year process of neuroendocrine changes that mark the beginning of adolescence and prepare individuals for sexual

reproduction. We then review evidence (and pinpoint knowledge gaps) about neural and social changes linked with puberty and internalizing disorders; details about the empirical studies cited are provided in the [Supplement](#). We propose a conceptual model that integrates across this evidence base, and conclude with suggestions for future research directions.

GROWING SEX DISPARITIES IN INTERNALIZING DISORDERS DURING ADOLESCENCE

Meta-analyses show that during adolescence, girls' risk for depression rises to twice or more that of boys, a disparity in both symptoms and diagnoses that peaks in middle to late adolescence and persists across most of the remaining lifespan [for a recent multinational meta-analysis, see (2)]. Most worry-related anxiety disorders also have median age of onsets in middle to late adolescence; social anxiety, panic, general anxiety, and posttraumatic stress disorders all increase from ages 13 to 18 years, and girls are also diagnosed with these disorders 2–3 times more often than boys (9–11). Meanwhile, nonsuicidal self-injury significantly increases in early adolescence but continues to emerge well into middle to late adolescence, where it exhibits peak prevalence and sex disparities (12,13). Experiencing a disorder like depression or anxiety in adolescence has high costs; it is associated with greater likelihood of recurrence (14–18) as well as a range of poor long-term outcomes spanning peer and family

relationships, physical health problems, health-risking behaviors, and impediments to educational and occupational attainment (19).

Cohort Effects

Layered atop these well-known developmental trajectories, a series of new findings indicate that rates of these adolescent-emergent mental health problems (depressive and anxiety disorders, nonsuicidal self-injury, and suicidal thoughts and behaviors) have been increasing worldwide, especially over the past decade, and most notably among girls (2,20–23). A full examination of possible factors contributing to these cohort effects is beyond the scope of this review, but increases in treatment seeking or primary care diagnoses are unlikely explanations (24); the social processes discussed in this review may provide one useful starting point for such an analysis. Regardless, this underscores the urgency of identifying mechanisms for these internalizing problems in adolescence as well as the associated sex disparities.

Puberty

Internalizing disorders are known to be associated specifically with pubertal processes over and above age, suggesting that the relationship is not due solely to psychosocial factors common to individuals at a chronologically defined stage of adolescence (25,26). These biological risk factors play out differently for girls and boys (18,27–29). For example, in girls, earlier pubertal timing and more rapid pubertal tempo (relative to same-age, same-sex peers) is associated with higher rates of depressive disorders in particular, as well as substance use disorders, eating disorders, and antisocial behavior (27,28,30). We focus on the gonadarcheal phase of pubertal development instead of the earlier adrenarcheal phase, which is largely about energizing growth [for a review, see (31)]. Meanwhile, gonadarcheal development fosters maturation into a sexual being, which incorporates a broader suite of social processes such as negotiating sexual feelings, sensitivity to status, intimate friendships, and romantic relationships (32,33). In addition, development of secondary sexual characteristics affects how adolescents are perceived by themselves and others and may contribute to adultification (when children are perceived as being older and less innocent), particularly for Black girls (33,34).

There are various theories about why early (or atypical) timing and tempo may produce risk for psychopathology. Some well-known psychosocial hypotheses include maturational deviance, developmental readiness, risky social contexts, and maturational compression [for a review, see (6)]. Maturational deviance focuses on the risks of off-time development (early and late). In contrast, early-maturing youths in particular may be unprepared (developmental readiness) or overexposed (to risky social contexts). Finally, maturational compression focuses specifically on faster progression through puberty than peers. These compelling psychosocial explanations would benefit from more explicit connection to neurobiological foundations, given that puberty encompasses both psychosocial and neurobiological changes. Meanwhile, neurobiological approaches have largely emphasized reward and positive

valence systems, alone or in conjunction with negative affect and emotion regulation [for reviews, see (11,35–38)]. These perspectives have tended to overlook many social processes like self-perception and mentalizing, or to simply subsume social processes within the affective and motivational aspects of experiences like rejection. The present model is an attempt to fill this gap, given that contributions from these other processes and systems have been well detailed elsewhere.

BRAIN DEVELOPMENT

There is a rich literature using animal models to reveal cellular mechanisms for puberty's effects on brain development, although a full review of this topic is outside the scope of this paper [for a comprehensive review, see (39)]. Briefly, gonadal steroids increase to adult levels (primarily estrogen and progesterone in girls and testosterone in boys, although all three increase in both sexes) and produce changes in adolescents' bodies and brains. Receptors for these hormones are found throughout the brain, particularly in the frontal cortex. Steroids can have long-term effects by regulating gene expression, or acute effects through second messenger cascades. Two key neural processes associated with puberty are dendritic spine turnover and increased inhibitory neurotransmission. Greater turnover (both loss and gain) of dendritic spines during a 24-hour period in adolescence compared with adulthood likely accommodates neuroplasticity and experience-dependent learning. Ovarian hormones in particular have been linked to the changes in balance of inhibition versus excitation in the frontal cortex.

Translating from the animal literature to humans has been a focus in the past decade. A recent systematic review catalogued evidence of associations between puberty and human brain structure, function, and connectivity (40). Most studies related brain structure or function to pubertal development when controlling for age, which is akin to modeling pubertal timing (i.e., pubertal stage relative to one's same-age peers). In general, prefrontal cortex (PFC) structure and function were most frequently linked with puberty. This may tentatively align with the insights about cellular processes discussed above. However, newer studies may refine that understanding. In a recent accelerated longitudinal dataset, pubertal development was found to be a better predictor of subcortical brain volume than age (41), and subcortical functional connectivity decreased with advancing pubertal stage in girls, which may reflect altered inhibitory neurotransmission and synaptic pruning with particular impact on frontostriatal functioning (42).

Brain Development as a Mediator of Puberty's Impact on Adolescent Mental Health

Despite growing evidence of pairwise puberty-brain associations, few studies have taken the more integrative step of empirically testing whether brain development mediates links between puberty and mental health outcomes. A pair of structural studies found that larger pituitary volumes mediated the relationship between early pubertal timing and increased depressive symptoms (43), as well as between greater dehydroepiandrosterone (DHEA) levels and social anxiety

symptoms (44). Hippocampal structure also mediated the link between greater testosterone levels for one's age and depressive symptoms in girls (45). Meanwhile, a recent large multisite sample of 14-year-olds observed that intrinsic functional connectivity of key nodes from the default mode network (DMN) decreased with puberty in girls (but increased with puberty in boys); weak connectivity of the perigenual anterior cingulate cortex in particular was associated with higher internalizing symptoms 2 years later, although mediation was not tested directly (46). This last result is particularly relevant given involvement of the DMN in social cognition broadly and the perigenual anterior cingulate cortex in adolescent self-perception specifically (47–49).

These initial efforts represent important proofs of concepts, but more needs to be done to identify neural mechanisms of the puberty-internalizing association in adolescence. A number of studies have examined adrenarche and related androgens such as DHEA, but expanding to focus on the gonadal phase of puberty is essential. Diversifying beyond structural metrics of brain maturation will also be particularly important in order to understand how these processes influence brain reactivity to particular classes of stimuli as well as intrinsic functional connectivity. Work relating puberty and intrinsic functional connectivity of the DMN is surprisingly sparse, given extensive evidence of the latter's role in internalizing (46). Based on the animal and human literature on pubertal-neural associations, we think that close attention to the frontal cortex (particularly at the midline), the DMN and salience networks, and is warranted (50).

SOCIAL PROCESSES

In addition to the neural changes linked to pubertal development, there are significant changes in a host of social processes across adolescence that unfold in tandem with ongoing "social brain" development (including cortical midline structures, the temporoparietal junction, and the anterior temporal cortex) (51–54).

Social Cognition

There is a substantial body of literature documenting changes in social cognition (self-perception and mentalizing) across adolescence. One focus has been on change in self-esteem trajectories across adolescence at both group mean and individual levels (55,56), with pronounced decreases specifically seen in girls (57). Studies have also documented increases across development in self-consciousness (58,59), self-complexity (60,61), and self-disclosure (62). Other research has suggested that mentalizing (cognitive perspective-taking) also continues to improve, as seen by increased accuracy and decreased reaction time on laboratory mentalizing tasks (63–65). Adolescents also self-report a greater tendency to take others' perspectives as they mature, an effect that is stronger for girls than boys (66).

Social Cognition and Mental Health. These developmental changes, particularly in self-perception, are thought to affect (and be affected by) adolescent mental health in transactional relationships over time. Low self-esteem and high self-consciousness are established prospective psychosocial risk

factors for adolescent depression (55,67–69). Several other studies have found that various facets of self-complexity prospectively predict depressive symptoms in adolescents (60,61). Furthermore, cognitive models of anxiety (particularly social phobia) propose that both self-focused attention and "construction of the self as a social object" maintain anxiety by increasing negative self-evaluations (70). Regarding mentalizing, some recent integrative theoretical frameworks point to this as an overlooked contributor to, and consequence of, adolescent mental illness (8). Empirical evidence on this point is more limited, although one recent study found that poor mentalizing abilities (about emotions and thoughts) may be associated with symptoms of withdrawal and/or depression in adolescents (64).

Social Cognition and Pubertal or Neural Changes. There is still limited empirical evidence directly linking puberty and changes in social cognition or its neural substrates, despite prominent theoretical proposals that they are intimately intertwined (52). One recent study found that increased negative self-evaluations were associated with both advanced puberty and severity of depressive symptoms (71). Neurally, self-reported pubertal stage tracked with an increased response in ventral striatum during third-person self-evaluation (a process that uses mentalizing to inform self-knowledge) (72); and over a 3-year period, greater advancement through puberty was associated with greater increases in ventromedial PFC (vmPFC) activity during social self-evaluations (48). Another study of adolescent girls found that anterior temporal cortex activation during social emotion processing (which implicated mentalizing) increased with hormone levels, independent of age (73). However, we recently observed no association between either age or puberty (self-reported stage or hormone levels) and vmPFC activation during self-evaluation in a well-powered cross-sectional study of early adolescent girls (74). Furthermore, most neuroimaging studies of social cognition have relied on chronological age to track maturation rather than pubertal stage. For example, increases in vmPFC have been found by age for both physical self-concept (75) and self-consciousness (76). In contrast, dorsomedial PFC activation during mentalizing decreases with age (73,77–79). In sum, most of these studies would benefit from replication in much larger samples and further incorporation of pubertal or hormonal measures.

Peer Relations

It is widely understood that peer relations are a major determinant of well-being and mental health in childhood and adolescence. In this section we focus on 3 facets of peer relations: peer rejection, close friendships, and romantic or sexual relationships. Together these represent highly salient/emerging developmental tasks in adolescence (80,81), reflecting the need to foster social connection with peers and minimize social rejection from them. Of course, the quality of family relationships is also well known to robustly affect adolescent mental health, such that family support buffers against risk and family conflict augments it (82–84), and many of the underlying mechanisms described here may apply to family interactions as well.

Peer Rejection. Rejection during adolescence is a powerful threat to mental health (85). Peer rejection experienced chronically and in the context of power imbalances is known as bullying or victimization, and adolescents who lack social support (especially those who lack a best friend) are more vulnerable to bullying (86). Being bullied from late childhood through mid-adolescence predicts risk for anxiety disorders through late adolescence and beyond (87). Similarly, chronic relational victimization is a consistent predictor of adolescent depression, temporally preceding it in many longitudinal studies (88), and interpersonal stressors, particularly peer rejection, are prominently associated with self-harm (89,90). For adolescent girls in particular, relational aggression is a common form of bullying (91) and a potent risk factor for internalizing problems (92).

Close Friendships. Although friendships emerge in childhood, building and strengthening close friendships are core developmental tasks of adolescence (80) and are considered to have a unique impact relative to broader markers of acceptance by the peer group (93). Recent research suggests that supportive close friendships can buffer against the harmful consequences of negative family relationships on mental health (94) and that close friendship strength during adolescence is related to physical and mental health more than a decade later (93,95). In addition, social support from close friends increases self-worth and buffers the effects of chronic peer rejection on internalizing (84,93,96) and decreased long-term well-being (97).

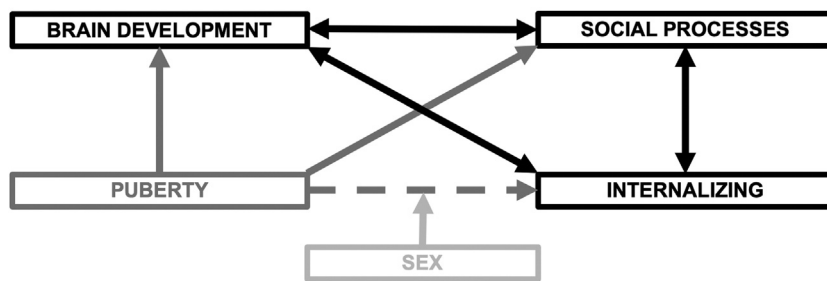
But some features of peer relationships, especially in adolescent girls' close friendships, may exacerbate risk for mental health problems (98). Notably, even positive features of close friendship quality may be associated with mental health risk by increasing socialization of depressive symptoms and self-harm behaviors (99,100), particularly in adolescent girls with a co-ruminative style (101,102). While self-disclosure to close friends is related to increased intimacy (103), it can also be related to current and future adolescent depression, as well as deliberate self-harm and suicidality (67,102,104). Co-rumination, or the tendency to extensively discuss problems in the context of a dyadic relationship, is more frequently seen in girls' close friendships and is more strongly related to increases over time in both internalizing symptoms and intimacy in adolescent girls' friendship dyads than in boys' (102). Taken together, the evidence suggests that close friendship quality is typically a protective factor against mental health problems in adolescence, but under certain conditions, close friendships may exacerbate internalizing problems in adolescent girls.

Romantic and Sexual Relationships. Romantic relationships represent an emerging developmental task in the latter half of adolescence, with >70% prevalence by the age of 17 years (81), and provide important learning experiences (105). Particularly for girls, romantic relationships are initially associated with increased internalizing symptoms, because they are new and stressful experiences (106). By late adolescence and beyond, however, romantic relationships frequently provide intimacy and support that exceeds that of close friends

(107). Although in adolescence, sexual activities are most frequently pursued in the context of romantic relationships, having sex outside of romantic relationships is increasingly frequent (108); these nonromantic sexual relationships can include "friends with benefits" and sometimes produce distress if they do not evolve into romantic relationships (109). Some features of romantic and sexual relationships (e.g., poor-quality relationships, breakups) are strongly associated with adolescent mental health outcomes (110). This ranges from depressive symptoms, particularly in girls (106,111), to self-harm and suicide risk (112–114). In these studies, the experience of being rejected has been found to be a particularly salient relationship stressor that acts as a precipitant of mental health problems.

Peer Relations and Brain Development. One of the most extensive lines of research in developmental social neuroscience has focused on neural responses to experiences of social exclusion, including in adolescents with internalizing disorders. Many studies use the virtual ball-tossing game Cyberball (115–118) or other interactive paradigms with adolescents (Chatroom, Virtual School) (37,119,120) to assess neural responses to ostensible experiences of acute social exclusion or social evaluation (rejection and acceptance feedback) by peers. Collectively, these studies demonstrate consistent evidence of engagement in the subgenual anterior cingulate cortex, ventrolateral PFC, posterior midline regions, and ventral striatum [for a meta-analysis, see (121)]; the paradigms that look at anticipation/receipt of social evaluative feedback additionally elicit responses in the amygdala and medial orbitofrontal cortex (37,119,120,122). A few studies suggested that activity in these regions produced by social exclusion or rejection feedback was associated with pubertal development (118,120) or predicted future depressive symptoms (117), but more work is needed to integrate across pubertal, neural, social, and internalizing processes. The anterior insula, part of the salience network, has also been implicated in atypical responses to social exclusion in depression (120,123) and anxiety (124), but the direction of effects has been mixed. Compared with both depressed adolescents and healthy control adolescents, adolescents who engage in self-harm likewise exhibit group differences in responses to social exclusion in the medial PFC, ventrolateral PFC, striatum, and insula (125,126).

Compared with this body of work, we know relatively little about how brain development relates to positive aspects of social connection, like close friendships. However, one recent study found that friendship buffers affective and neural responses to social exclusion in adolescents who experienced early adversity (127). Another recent study showed that choosing to self-disclose about intimate information to a close friend was associated with increased activity in regions associated with social cognition and emotion regulation, including the vmPFC, for adolescent girls (128). There is likewise very little information about neural changes accommodating the emergence of romantic or sexual relationships in adolescence, and the few neuroimaging studies in this area mainly focus on sexual risk taking (32).



depicted. Note that neither the brain's initial trigger of puberty nor social experiences that affect pubertal timing, such as early-life adversity, are depicted here as double-headed arrows owing to the specific focus on processes happening throughout adolescence.

Figure 1. Heuristic conceptual model of neural and social mechanisms for the impact of pubertal development on adolescent mental health. The dashed arrow represents mediation of the puberty–internalizing link via neural and social mechanisms. Double-headed arrows represent transactional processes unfolding over time across adolescence. Sex is depicted as a known moderator of the puberty–internalizing link; it is expected to moderate the other paths in this model (e.g., puberty–brain development, puberty–social processes, social processes–internalizing), but for clarity's sake that is not

Peer Relations and Puberty. In contrast to its under-examined associations with brain development, romantic and sexual relationships are frequently characterized as a salient consequence of puberty (129). Adolescent romantic relationships and behaviors are qualitatively different than the feelings that prepubescent children can have toward their peers (107,130); testosterone and estradiol seem to underlie some of that romantic interest (131). Importantly, although sexual reproduction can be considered the ultimate evolutionary target of pubertal development, reproductive success encompasses a much broader range of social processes than sexual reproductive capacity per se (32,132). In this sense, romantic and sexual relationships represent a primary and highly developmentally salient context in which the social changes of adolescence reveal themselves. In contrast to this work on romantic/sexual relationships, there is a relative dearth of information relating close friendships to pubertal development, although one study found early-maturing girls to be more likely to experience dissolution of a friendship (133). Work in this area tends to look at puberty's relations to a broader category of peer stress (134). Peer rejection is one type of peer stressor in this category. Much of the work on peer rejection and puberty has typically investigated the latter as a moderator of the association between social victimization and mental health, consistent with the contextual amplification model, which posits that off-time maturation acts to amplify the negative impact of stressful social contexts (135,136).

CONCEPTUAL MODEL

The literature reviewed above suggests that there is a convincing pattern of associations between puberty, brain development, social processes (social cognition and peer relations), and adolescent-emergent internalizing disorders. Our model proposes that puberty dramatically alters adolescents' social perceptions and experiences with peers. It does so via physical, neural, and interpersonal changes that reshape how adolescents see themselves and how they interact with others. Thus, in contrast to contextual amplification theory (135), which casts puberty in a moderating role, we propose direct and indirect effects of pubertal (and neural) changes on social processes and mental health (see Figure 1).

Another central feature of our model is a consideration of how social, neural, and pubertal processes co-evolve across the duration of adolescence (see Figure 2 for alignment of

these processes with mental health trajectories). For example, most significant changes in secondary sexual characteristics finish in mid-adolescence, but hormone levels continue to rise through late adolescence, just as do changes in brain structure, function, and connectivity. In the social sphere, early adolescence is characterized by changes in self-perception, as well as an emphasis on avoiding social rejection by the peer group. By mid-adolescence, more advanced perspective-taking tendencies and mentalizing abilities largely plateau, except for some very complex or highly recursive tasks. At this time, new forms of social connection with peers emerge, namely romantic and sexual relationships, and through late adolescence they play increasingly prominent roles as sources of support and contexts of important learning experiences. These social developmental trajectories shape the unfolding of transactional processes in our model across the second decade of life.

Each social advance sets the tone for subsequent changes—social cognitive predispositions adjust the probability of success or failure in peer relations, and the resulting social experiences also shape the brain and affect mental health. In other words, social experiences across adolescence are not only predictive of concurrent and near-future mental health, but also part of a cascading series of developmental and risk processes that are driven at least in part by earlier biological and psychosocial changes. Through such interactions, this dynamic system can augment or buffer against risk for mood and anxiety disorders. While these neural and social consequences of puberty for internalizing may be most pronounced in girls, they are still expected to affect boys.

For this work to progress our scientific models must have testable, falsifiable hypotheses (137). Key examples of testable and falsifiable hypotheses in our integrative model include the following: 1) features of brain development or social processes mediate the association between pubertal development and internalizing; 2) there are specific temporal sequences to these effects, particularly social ones (e.g., that self- and social cognition-related processes have greater impact in early to middle adolescence, while close friendships or romantic relationships have greater impact in late adolescence); and 3) these effects proceed along specific paths (e.g., competing mediations through puberty within the adolescent period are not supported). While some of these have begun to be tested as reviewed above, many require special types of designs (e.g., longitudinal) to be adequately evaluated.

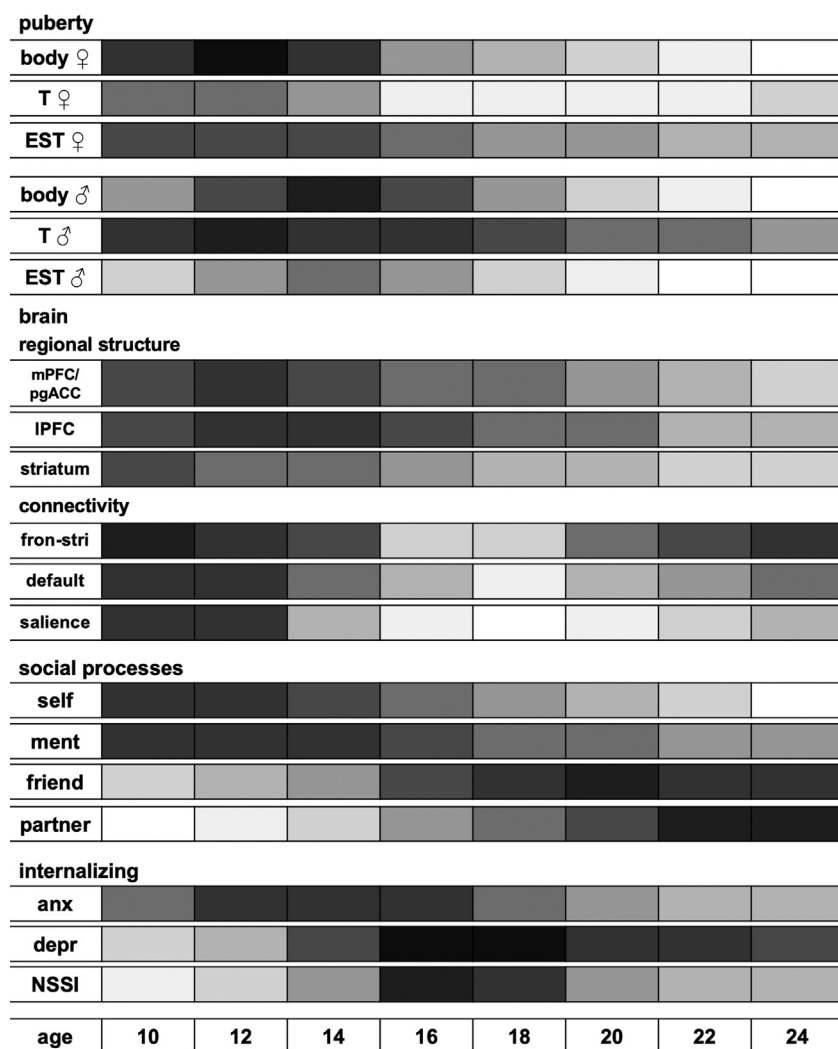


Figure 2. This chart depicts the degree of dynamic developmental relevance for each process or system, aligned by chronological age. The values were determined by qualitatively aggregating from the literature referenced in our manuscript, including empirical studies reported on in reviews that we cited. Each bar represents a 2-year age window across adolescence, from 10–11 years to 24–25 years. Color is saturated in 10% intervals ranging from 0% to 100% saturation (low to high plasticity, respectively). For example, the rapid development of secondary sex characteristics (bodily changes) in early to middle adolescence is conveyed by the highly saturated values during those age windows. Saturation values do not represent levels or prevalence rates of the process or system. For example, the slope of increase in testosterone (T) is steepest in early adolescence, as represented by high saturation values, even though absolute levels of testosterone do not peak at the youngest ages. We note that the emphasis is on the relevance of each process or system in developmental tasks across an age cohort, rather than on an individual level. In other words, testosterone remains influential on social behavior in late adolescence and beyond, but this is due to individual differences rather than development. We also note that there are well-documented shifts in pubertal timing such that some racial/ethnic identity minority adolescents (Black and Latino) enter puberty earlier than others (non-Latino White and Asian). Finally, in contrast to pubertal processes and internalizing, saturation values for resting-state functional connectivity networks (default mode, salience) and social processes were heavily based on cross-sectional studies and therefore caution is warranted during interpretation until these patterns are confirmed in longitudinal samples. ♀ indicates female; ♂ indicates male. anx, worry-based anxiety disorders; default, default mode network; depr, depression; EST, estrogen; friend, close friendships; fron-stri, frontostriatal connectivity; IPFC, lateral prefrontal cortex; ment, mentalizing; mPFC, medial PFC; NSSI, nonsuicidal self-injury; pgACC, perigenual anterior cingulate cortex; salience, salience (cingulo-opercular) network; partner, romantic and sexual relationships.

FUTURE DIRECTIONS

One future direction with strong implications for both mental health and social processes is to understand the role that digital devices and social media play in these processes—a pressing question to which individuals, families, schools, policy makers, legislators, and digital designers are all demanding answers (20). However, the scientific literature on this topic to date has generally been of mixed quality and conclusions (138). Of course, one of the key functions of digital technology for adolescents in particular is social connection via social media and other communication platforms. As such, an especially important consideration is how social connection is experienced in the context of digital technology and social media, and how this might influence mental health in light of the material reviewed previously about the dual-edged nature of close relationships.

In addition, the biological changes of adolescence do not cease when puberty concludes; rather, the brain continues to

exhibit change in structure and function across the entire duration of adolescence, reaching developmental asymptotes largely in the mid-twenties (139). Despite the completion of many of the morphological changes associated with puberty-related development of secondary sexual characteristics, rendering self-report metrics ineffective, hormone levels continue to rise across the same extended period as brain development (31). These ongoing increases in sex hormones also are thought to shape and refine neural circuitry as well as drive many late-maturing events not captured by categorical Tanner stages. In this respect, hormone levels may serve as a better index of maturation to incorporate during the latter half of adolescence, as well as a measure of individual differences relating to social changes and mental health (40).

While neuroimaging studies have increasingly assayed sex hormones, many studies relating puberty to mental health draw on large nationally representative samples that are typically limited to self-report and thus unable to examine later

contributions of hormonal changes. This limitation is counterbalanced by the ability of nationally representative studies to contextualize these associations across sex and ethnicity, something that most neuroimaging work has yet to be able to do. We hope that a move toward more multilevel, longitudinal work will make progress toward these open questions, which is happening in medium-sized cohorts ($N \approx 100\text{--}300$) (140) as well as large ones ($N > 1000$ s) (141,142). A trend that we hope spreads widely is for studies to harmonize data collection efforts, with an aim to truly complement and inform each other. For example, medium- and smaller-sized studies may be more nimble and suited to achieve deep phenotyping, while larger studies contribute breadth and generalizability.

Finally, pubertal-social-internalizing links have been more extensively studied in girls, which clearly calls for more work to understand these interactions in boys. For example, there is mixed evidence on whether and how atypical tempo or timing of pubertal maturation may affect boys' mental health; it may have different negative consequences than for girls, possibly oriented more toward externalizing (29,143). One reason for the lagging understanding of these processes in boys is that measuring puberty via the oft-used self-report scales may be less precise for boys than girls (144). As noted in the legend of Figure 1, future research should explore which of the potential moderating influences of sex are fundamental (i.e., mechanistic) versus epiphenomenal.

CONCLUSIONS

The evidence presented in this review suggests that puberty launches a concert of neural and social changes that individually and together affect adolescent propensity for internalizing disorders, particularly for girls. Over time, these neural, social, and mental health processes interact in a transactional manner to mutually shape trajectories of risk or resilience. A major goal of our proposed model is to highlight the central role of social processes, particularly related to the progression of changes from social cognition to social connection. Incorporating a focus on social processes across different phases of adolescence in these multilevel studies is a high priority for future research, particularly in studies using biomarkers of neural or pubertal development. To truly advance the field, we should endeavor to design integrative approaches that measure these domains across multiple levels and within individuals over time.

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ARTICLE INFORMATION

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