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Puberty and Gonadal Hormones: Role in Adolescent-typical Behavioral Alterations

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Abstract

Adolescence is characterized by a variety of behavioral alterations, including elevations in novelty-seeking and experimentation with alcohol and other drugs of abuse. Some adolescent-typical neurobehavioral alterations may depend upon pubertal rises in gonadal hormones, whereas others may be unrelated to puberty. Using a variety of approaches, studies in laboratory animals have not revealed clear relationships between pubertal-related changes and adolescent- or adult-typical behaviors that are not strongly sexually dimorphic. Data reviewed suggest surprisingly modest influences of gonadal hormones on alcohol intake, alcohol preference and novelty-directed behaviors. Gonadectomy in males (but not females) increased ethanol intake in adulthood following surgery either pre-pubertally or in adulthood, with these increases in intake largely reversed by testosterone replacement in adulthood, supporting an activational role of androgens in moderating ethanol intake in males. In contrast, neither pre-pubertal nor adult gonadectomy influenced sensitivity to the social inhibitory or aversive effects of ethanol when indexed via conditioned taste aversions, although gonadectomy at either age altered the microstructure of social behavior of both males and females. Unexpectedly, the pre-pubertal surgical manipulation process itself was found to increase later ethanol intake, decrease sensitivity to ethanol's social inhibitory effects, attenuate novelty-directed behavior and lower social motivation, with gonadal hormones being necessary for these long-lasting effects of early surgical perturbations.

Keywords

adolescence; alcohol; gonadal hormones; novelty; puberty; social behavior; stress; testosterone

Puberty versus Adolescence

Although the terms adolescence and puberty are often used interchangeably, these terms are not synonymous. Typical changes associated with puberty include increases in gonadal steroid levels, physical signs of sexual maturation such as the emergence of secondary sex characteristics, as well as behavioral alterations including increased interest in the opposite sex and sexual desire. Adolescence, on the other hand, is a broader developmental period subsuming the interval between childhood and adulthood. During this interval, reproductive maturation occurs at some point, along with maturational changes in cognitive and

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emotional functioning, and the acquisition of new social skills to facilitate survival away from parents. This gradual transformation from immaturity/dependence to maturity/independence is a developmental phase that can be identified across different mammalian species (Spear, 2007), with adolescent animals often differing notably from those younger or older in the ways they respond to and interact with stimuli in their environment (Spear, 2000).

While there is no single biological event that signals its onset or offset, adolescence in humans is often considered to subsume the second decade of life, with females tending to mature earlier than males (Petersen et al., 1996). Some adolescent-typical characteristics have been found to persist into at least the mid-twenties, a period sometimes termed "emerging adulthood" (Arnett, 2000; Feldman and Elliot, 1990). Likewise, in rats, a conservative age range during which both males and females appear to exhibit adolescent-typical neurobehavioral characteristics has been defined as postnatal (P) day 28-42 (Spear and Brake, 1983; Spear, 2000; Odell, 1990), although females tend to progress into adolescence slightly earlier, and animals of both sexes, especially males, continue to show some signs of adolescence for some time thereafter. Given the broad developmental periods subsumed, adolescence has been subdivided into early, mid and late stages. In humans, these stages are thought to refer to approximately 10-14 years (early), 15-17 years (mid), 18-25 years (late/emerging adulthood) (e.g., Baumrind, 1987; Feldman and Elliot, 1990; Arnett, 2000), with specific physical, hormonal, and neurobehavioral changes associated with each phase (Feldman and Elliot, 1990). In rats as well, it has recently been suggested that the period between P28 and P42 be considered early-mid adolescence, with the interval between approximately P42 and P55 viewed as more analogous to the late adolescence/emerging adulthood period in humans (Vetter-O'Hagen and Spear, 2011a).

Although in some individuals the onset of adolescence seems contemporaneous with the emergence of certain signs of puberty (e.g., Petersen et al., 1996), the timing of puberty has been shown to vary markedly within the broader adolescent period (e.g., Dubas, 1991), with both early or late pubertal onset associated with differences in later social and physiological functioning. For instance, early pubertal maturation relative to one's peers has been associated with increases in substance use and delinquency in both sexes (e.g., Negriff et al., 2010; Michaud et al., 2006) and an increased risk for the development of later affective disorders in women (Zehr et al., 2007; Ge et al., 2001). Late puberty in boys has also been associated with increased antisocial behavior (Waylen and Wolke, 2004). Among children in the United States, the mean age of entering puberty in girls is approximately 11 years of age, continuing to completion by approximately 16 years of age; in boys this process is slightly delayed, beginning around age 12 on average and ending by about 17 years old, but with substantial individual variation in both the age of onset and progression through the stages of puberty within the broader adolescent period (Sun et al., 2002). In rats, the peripubertal period can be considered to subsume from about P30-40 in females and P35-55 in males (Ojeda and Skinner, 2006), with physical markers of sexual maturation emerging around P32-36 and P40-48 in females and males, respectively (Lewis et al., 2002; Vetter-O'Hagen and Spear, 2011). For instance, in the Vetter-O'Hagen and Spear (2011a) study, vaginal opening in Sprague-Dawley female rats was not evident at P28 but had occurred in some females by P32, with all showing vaginal opening at P36; in males, balano preputial skinfold separation and the presence of sperm in the seminiferous tubules were observed in a majority of males by P40, with these indices of pubertal maturation generally complete by P44. In this study, gonadal hormones showed similar, albeit somewhat delayed ontogenetic patterns, with estradiol and progesterone levels in females detectable at the youngest age examined (P28) and gradually rising across age to reach adult-typical levels by P48, whereas testosterone levels were not significant until P40, increasing thereafter.

Adolescent-typical Neurobehavioral Changes

In contrast to the relatively clearly defined and temporally restricted period of puberty, the broader period of adolescence has no obvious biological events to signal its onset or offset. During adolescence, there is considerable remodeling in cortical and limbic brain areas, along with decreases in brain energy utilization, selective synaptic pruning and myelination of axons (see Bava and Tapert, 2010; Brenhouse and Andersen, 2011; Spear, 2010; Sturman and Moghaddam, 2011, for review).

Regionally-specific structural and functional changes in the balance between limbic and prefrontal structures, including delayed maturation of inhibitory “top-down” control regions in the prefrontal cortex, have been postulated to contribute to enhanced activity in subcortical limbic regions (e.g. nucleus accumbens; amygdala) important in the processing of natural rewards including social and novel stimuli, as well as alcohol and other drug rewards (see Casey et al., 2008; Somerville et al., 2010, for review). Concomitant with these neural changes, a variety of behavioral alterations are evident in both human adolescents as well as adolescents of other species, including increases in social interactions, elevations in novelty-seeking, and experimentation with alcohol and other drugs of abuse (e.g.,Doremus-Fitzwater et al., 2010; Spear, 2010, 2011).

For instance, levels of sensation-seeking and motivation to experience new stimuli have been shown to peak at 12-15 years of age and to decline thereafter into adulthood (Steinberg et al., 2008), with such sensation seeking highly correlated with novelty approach preference in humans (McCourt et al., 1993). Likewise, novelty-directed behavior was observed to peak at P32-36 in rats at levels greater than at younger or older ages (Vetter-O’Hagen and Spear, 2011), with a variety of experimental paradigms showing enhanced responding to and interacting with novelty in adolescent rodents relative to adults (Adriani et al., 1998; Belluzzi et al., 2004; Caster et al., 2007; Collins and Izenwasser, 2004; Douglas et al., 2003; Philpot and Wecker, 2008; Stansfield and Kirstein, 2006, but also see Cao et al., 2007; Caster et al., 2005). Adolescent male rats not only interact more with novel objects than do adults, but they also find these interactions with novelty to be more rewarding than do their adult counterparts (Douglas et al., 2003).

Adolescence is also characterized by high levels of ethanol use, with approximately 11% of 8^{th} graders, 22% of 10^{th} graders and 25% of high school seniors in the United States reporting a binge pattern of drinking (i.e., consumption of 5 or more drinks per occasion) in the last 2 weeks (Johnston et al., 2007), and even more elevated rates of binge drinking are reported among adolescents in many European countries (Ahlström and Osterberg, 2005). On average, adolescents drink more than twice as much per drinking episode as adults (Substance Abuse and Mental Health Services Administration, 2006). High levels of ethanol consumption are not restricted to human adolescents but may be seen in other mammalian species as well, with adolescent rats typically drinking 2-3 times more ethanol relative to their body weights than adults (Brunell and Spear, 2005; Doremus et al., 2005; Vetter et al., 2007; Vetter-O’Hagen et al., 2009). These relatively high g/kg intakes typical of adolescent rats decrease dramatically in males across the adolescent to adult transition, reaching a plateau during early and mid adolescence (P28-39) and declining around P40 to reach intakes modestly elevated over adult-typical consumption levels, with drinking gradually declining thereafter to reach adult-typical intakes by approximately P70 (Vetter et al., 2007).

High levels of ethanol intake observed during adolescence may be related, at least in part, to adolescent-typical insensitivities to a number of adverse alcohol effects that may normally serve to moderate intake (Spear and Varlinskaya, 2010). For instance, adolescent rats are considerably less sensitive than their adult counterparts to ethanol-induced social inhibition

(Varlinskaya and Spear, 2002), sedation (Draski et al., 2001: Moy et al., 1998; Silveri and Spear, 1998), motor impairment (Ramirez and Spear, 2010; White et al., 2002) and even hangover effects (Doremus et al., 2003; Varlinskaya and Spear, 2004). Adolescent rats are also less sensitive to ethanol-induced taste aversions relative to more mature animals (Anderson et al., 2010; Vetter-O'Hagen et al., 2009).

In contrast to their relative insensitivity to adverse and intoxicating effects of ethanol that may serve to moderate intake, adolescent rats (like their human counterparts -- e.g., Beck et al., 1993) conversely are extremely sensitive to low doses of ethanol in terms of social facilitation, showing marked ethanol-induced social activation that is not normally evident in adult rats (Varlinskaya and Spear, 2002, Spear and Varlinskaya, 2005). More recent studies have demonstrated that adolescents also find alcohol more rewarding than do adults (e.g., Pautassi et al., 2008). Such enhanced sensitivity to the socially activating and rewarding effects of ethanol may also contribute to the elevated ethanol intake of adolescents.

Puberty-dependent and –independent Neurobehavioral Changes

Some adolescent-typical neurobehavioral alterations may depend upon the rise in gonadal hormones at puberty, and hence would be considered puberty-dependent. Other neural changes, particularly in hypothalamic and associated forebrain regulatory regions, may predate puberty and may serve to trigger the hormonal reawakening of puberty (e.g., Ahima et al., 1997; Chehab et al., 1997; Irwig, et al., 2004; Navarro et al., 2004). Yet other neurobehavioral alterations may be driven by more general, puberty-independent ontogenetic processes occurring during adolescence. The extent to which specific adolescent-typical neurobehavioral characteristics are puberty-dependent or independent is an area of active inquiry, with increasing attention being focused on this topic. While challenging to parse the relative contributions of pubertal versus non-pubertal maturation processes to adolescent-typical neurobehavioral alterations in human subjects, this distinction is beginning to be addressed by relating different measures of interest not only to chronological age, but also to objective indices of pubertal development, such as Tanner's stage classification of secondary sex characteristics (Marshall and Tanner, 1968), or subjective self-report measures such as the Pubertal Development Scale (Martin et al., 2002). Using such approaches, for example, adolescent-typical increases in sensation-seeking have been suggested to be pubertally-related in humans, based on findings that self-reported sensation seeking was highly correlated with pubertal stage, but not age, when examining individuals varying widely in pubertal status across a relatively narrow age range (11-14 years old; Martin et al., 2002). The results of similarly designed studies have provided some initial support for the suggestion that pubertal status may also play a role in cognitive processing of emotion and social stimuli as well as in motivation and arousal (Blakemore et al., 2010; Forbes and Dahl, 2010; Dahl and Gunnar, 2009; Steinberg, 2008). It can nevertheless be challenging to parse the relative contribution of pubertal status versus age in these studies, especially when, as in the majority of these studies, the subjects examined were similar in chronological age, but varied markedly in pubertal status, thereby biasing for detection of pubertal status effects over age effects (see Spear, 2009 for discussion). Moreover, given well-known individual differences in developmental rate, age likely provides at best only a modestly effective proxy for non-pubertal-related maturational status, further complicating attribution of developmental changes into those that are related to puberty versus those that are non-pubertal in origin.

In animal models, examining puberty-dependent versus puberty-independent neurobehavioral changes can be systematically examined through pre-pubertal removal of the gonads, thereby creating animals that do not experience the increases in gonadal

hormones associated with puberty. Most of this work has focused on the role of rising levels of pubertal hormones for organizing neural substrates underlying adult sex-typical behaviors. Indeed, this approach has revealed notable effects of pre-pubertal gonadectomy on later expression of a variety of adult-typical, sexually dimorphic behaviors, including reproductive behavior, aggression, and anxiety-related behaviors in adulthood (Schulz and Sisk, 2006; Romeo et al., 2003; Primus and Kellogg, 1989, 1990).

Few studies, however, have used this strategy to examine the role of rising gonadal hormones on normal post-adolescent declines in adolescent-typical behavioral characteristics, and among these studies, only limited evidence at best has emerged for a role of gonadal hormones in the emergence of adult-typical responding associated with the normal age-related declines in characteristic adolescent behaviors. For instance, in rats, the ontogeny of play fighting shows an inverted U-shaped pattern that rises to plateau around P30-35 and declines thereafter (Panksepp, 1981; Thor and Holloway, 1984; Vanderschuren et al., 1997; Varlinskaya and Spear, 2008; Varlinskaya et al., 1999). To the extent that pubertal increases in gonadal hormones play an inhibitory role in this behavior, pre-pubertal gonadectomy would be expected to block developmental declines in this behavior. Yet, pre-pubertal gonadectomy of males at P22 was found to notably reduce play fighting between P31 and P35 (at a time when testosterone levels in intact males are very low) rather than to delay the ontogenetic decline in this behavior as might have been expected (Cooke and Woolley, 2009).

Using a variety of approaches, a number of other studies in laboratory animals have revealed no clear association between puberty and adolescent- or adult-typical behaviors that are not strongly sexually dimorphic. For instance, in a recent study where we examined the relationship between hormonal, physical and behavioral measures during ontogeny in intact rats, no significant correlations emerged between hormonal or physical signs of pubertal development and novelty-seeking, with novelty-directed behaviors peaking at P32-36 and declining thereafter in both males and females despite the notable sex difference in pubertal status seen at this time (Vetter-O'Hagen and Spear, 2011a). Other studies as well have reported a lack of significant sex differences in ontogenetic patterns of novelty-directed behaviors in rats (Douglas et al., 2003; Abreu-Villaca et al., 2006), providing further evidence that increases in novelty-directed behavior during adolescence are not directly related to puberty. That is, if pubertal changes played a major role in this behavior, sex differences would be expected, with females showing a different ontogenetic profile than males due to their earlier progression through puberty. Additional evidence in females supporting the suggestion that gonadal hormones do not play a major role in modulating novelty-directed behavior during adolescence or in adulthood emerged in the same study when examining the impact of phase of estrous on novelty-directed and activity behaviors in vaginally open adolescent and adult females, with phase of estrous having no influence on these behaviors. Likewise, gonadectomy performed either pre-pubertally (P23) or in adulthood (P70) was found to have no impact on responses to novelty in either male or female rats (Vetter-O'Hagen and Spear, 2012). Thus, in the research conducted to date, the presence of gonadal hormones was found to have little impact on novelty-directed behaviors in rats during adolescence or in adulthood.

Some effects of gonadal hormones have emerged in work exploring effects of pre-pubertal or adult gonadectomy on ethanol intake (see Table 1 for summary). These effects, however, were found to be generally modest, primarily evident in males, and largely related to activational effects of gonadal hormones in adulthood rather than organizational influences exerted during the pubertal period. Pre-pubertal gonadectomy was not found to influence ethanol consumption and preference during adolescence: both male and female castrates demonstrated adolescent-typical elevations in ethanol intake that did not differ from that of

sham control animals (Vetter-O'Hagen and Spear, 2011b). However, effects on ethanol intake emerged when pre-pubertally gonadectomized males were tested during adulthood, with early gonadectomized males demonstrating increased ethanol intake and preference relative to their sham counterparts. Importantly, however, male rats gonadectomized in adulthood also demonstrated increases in ethanol intake (Vetter-O'Hagen and Spear, 2011b). Similar to these findings, recent work from another laboratory also found that preweanling gonadectomy in Long Evans rats increased ethanol consumption in adult males relative to their sham controls (Sherrill et al., 2011). In the Sherrill et al. (2011) study, animals similarly gonadectomized in adulthood were not included, leading the authors to conclude that the effects of pre-pubertal gonadectomy on adult ethanol consumption were likely due to organizational effects exerted by gonadal hormones during puberty. The results of the Vetter-O'Hagen and Spear study (2011b), which included an adult gonadectomized group, however, showed that similar increases in ethanol intake were also seen in male rats that were not gonadectomized until adulthood. Thus, without testicular hormones, regardless of whether gonadectomy occurred prior to puberty or in adulthood, adult male rats tended to display more adolescent-typical levels of ethanol consumption and preference in adulthood. These findings suggest that the ontogenetic decline in ethanol intake observed around P40 in males (Vetter et al., 2007) may be related to rises in pubertal hormones, with testicular hormones playing a possible suppressant role on drinking.

Given that the increased ethanol intake and preference seen in gonadectomized males by Vetter-O'Hagen & Spear (2011b) was evident regardless of the developmental period in which testicular hormones were removed, these results are more consistent with an activational rather than organizational role of testosterone and/or testicular hormones. Additional support for an activational rather than organizational effect of gonadal hormones on ethanol consumption was obtained in a follow-up study which replicated the enhancement of ethanol intake in males following gonadectomy in adulthood, and found that replacement of testosterone in male castrates was sufficient to return drinking behavior to levels comparable to those of sham control males (Vetter-O'Hagen et al., 2011). Yet, a potential organizational influence of pubertal testosterone cannot be completely dismissed because ethanol intake was not examined in pre-pubertally gonadectomized, adult testosterone-replaced males. Thus, it is possible that the presence of testosterone at puberty could serve to organize sensitivity of brain regions implicated in ethanol intake to later testosterone to activate male-typical ethanol drinking patterns in adulthood. This scenario would be similar to studies which show that pubertal exposure to testosterone acts to "organize" the ability of testosterone to "activate" adult-typical sexual behavior (e.g., Schulz et al., 2009).

The means by which testosterone and/or testicular products may influence ethanol consumption in males is still unknown. Although ethanol intake is often negatively associated with sensitivity to the intoxicating/aversive effects of ethanol and (more modestly) positively associated with ethanol's rewarding properties (e.g., Green and Grahame, 2008), gonadectomy-related increases in ethanol drinking in males do not appear to be associated with a decrease in sensitivity to aversive properties of ethanol when indexed via conditioned taste aversions (Morales and Spear, 2012). Likewise, neither pre-pubertal or adult gonadectomy altered sensitivity to the suppression of social behavior and social avoidance induced by a moderate (1 g/kg) dose of ethanol, although the microstructure of social behavior was altered, with gonadectomy at either age proportionally decreasing the frequency of social investigation while increasing frequency of contact behavior relative to sham control animals in both males and females (Vetter-O'Hagen and Spear, 2012).

An alternative possibility is that the increases in ethanol intake seen after pre-pubertal and post-pubertal gonadectomy in adult males may reflect alterations in the rewarding properties

of ethanol, with a testosterone-related suppression of ethanol reinforcement and/or ethanol-induced social facilitation perhaps tempering levels of ethanol intake typically seen in intact adult males. Work to address this possibility is underway. While it remains unclear exactly how sex steroids might influence the reinforcing and socially activating properties of ethanol, these effects could be exerted via androgen action on two major brain substrates implicated in the acute stimulatory and reinforcing effects of ethanol, the mesocorticolimbic dopamine system and the extended amygdala (McBride et al., 1999; Koob, 2003). Indeed, androgen receptors (AR) are located on midbrain dopamine neurons in regions such as the ventral tegmental area (Sato et al., 2008) that project to mesostriatal and mesolimbic structures (Creutz and Kritzer, 2004) strongly implicated in ethanol reinforcement (de Souza Silva et al., 2009) and social reward (Sato et al, 2008), thereby providing an opportunity for androgens like testosterone to modify brain reward systems, in turn altering socially facilitating and rewarding properties of alcohol and its consumption (Witt, 2007).

Effects of Early Surgical Manipulation

Our gonadectomy studies revealed unexpected and robust effects of the early (pre-pubertal) surgical manipulation process itself on later ethanol intake and sensitivity (see Table 2 for a summary of the major findings). Early sham controls demonstrated elevated levels of ethanol intake and enhanced ethanol preference in adulthood relative to both late sham controls (i.e., shams surgically manipulated in adulthood), as well as non-manipulated males, whereas similar trends in females did not reach significance (Vetter-O'Hagen and Spear, 2011b). This effect did not emerge until testing in adulthood, with neither gonadectomy nor sham surgery influencing ethanol intake or preference in males and females tested during adolescence. Likewise, early sham surgery also influenced ethanol sensitivity in adulthood, with the early sham manipulation (but not early gonadectomy, late sham surgery or late gonadectomy) eliminating ethanol-induced decreases in social preference in both sexes (Vetter-O'Hagen and Spear, 2012). This attenuation in the socially suppressing effects of ethanol by early sham surgery may have contributed in part to the elevation in ethanol intake seen in these males, although this is clearly not the sole driving force leading to elevated intake, given that early sham surgery attenuated ethanol-induced social suppression but did not influence ethanol intake in females. The process of early surgical manipulation not only influenced later ethanol intake and sensitivity but also altered novelty-directed behavior and social motivation, with early sham surgery decreasing responsiveness to novelty and motivation for social contacts as well (Vetter-O'Hagen and Spear, 2012).

Although the critical contributors to these early surgical manipulation effects are unknown, it seems plausible that they may be associated with the stress of this manipulation among juvenile animals. Indeed, animals in the early surgery conditions were manipulated at P23 – i.e., during the juvenile period between conventional weaning (P21) and the traditionally defined onset of adolescence (i.e. ~P28, see Spear, 2000). Numerous studies have shown that early life stress can alter ethanol drinking and sensitivity as well as anxiety behaviors in adulthood (e.g., Cruz et al., 2008; Huot et al., 2001; Rockman et al., 1987; Chester et al., 2008; Tsoory et al., 2007; Bazak et al., 2009; Toth et al., 2008). For example, in terms of ethanol drinking, exposure to stressors during adolescence, but not during adulthood, was found to elevate later adult drinking behavior relative to non-stressed controls in both sexes (Chester et al., 2008). In young rodents, maternal separation stress has repeatedly been shown to increase ethanol consumption in adulthood (Cruz et al., 2008; Huot et al., 2001; Rockman et al., 1987). Stressor exposure during early adolescence has also been shown to increase startle response and anxiety-like behavior on the elevated plus maze and decrease exploratory behavior in the elevated plus maze and in a novel environment when tested in adulthood (Bazak et al., 2009; Avital and Richter-Levin, 2005; Jacobson-Pick and Richter-

Levin, 2010). The latter of these effects of stressor exposure are in line with our results that demonstrated suppression of novelty-directed behaviors following early surgical manipulation in both sexes (Vetter-O'Hagen and Spear, 2012). Whatever the cause of these surgical manipulation effects, it is noteworthy that these early surgical effects on novelty-directed behavior, social motivation, and ethanol sensitivity were not evident following pre-pubertal gonadectomy, suggesting that gonadal hormones may be necessary for the later expression of these consequences of early surgical perturbation. In other words, it is possible that early removal of sex hormones through gonadectomy could act as a protective mechanism against the influence of early stressful events on ethanol intake and sensitivity as well as anxiety-like behavior, suggesting that long-lasting effects of early stressors necessitate an interaction between the hypothalamic-pituitary-adrenal (HPA) axis and the hypothalamic-pituitary-gonadal (HPG) axis during puberty. If this is indeed the case, then adult animals that undergo early gonadectomy followed by gonadal hormone replacement during adolescence should demonstrate elevations in ethanol intake and alterations in anxiety-like behavior similar to those observed in early sham-manipulated animals.

The unexpectedly robust effects of early sham surgery, although consistent with other evidence that exposure to stressors during development can exert long-lasting influences on ethanol intake and sensitivity, nevertheless complicate attempts to assess consequences of early gonadectomy and provide strong impetus for inclusion of non-manipulated control groups in such studies.

Conclusion

Taken together, the data reviewed here suggest surprisingly modest and nuanced effects of gonadal hormones on alcohol intake, alcohol preference and novelty-directed behaviors. Few gonadectomy effects were evident in females, although it should be cautioned that this could be related in part to the relatively high residual estradiol levels seen post-gonadectomy in our animals. In males, gonadectomy was found to increase ethanol intake in adulthood following surgery either prepubertally or in adulthood, with these increases in intake largely reversed by testosterone replacement in adulthood, thereby supporting an activational role of androgens in moderating ethanol intake in males. Thus, although there is compelling evidence that rising hormone levels during puberty organize brain regions responsible for adult-typical reproductive and related sexually-dimorphic behaviors (e.g., see Schulz et al., 2009 for review), gonadal hormones may be less relevant for the rise or developmental decline in certain other adolescent-typical behaviors, with these behaviors instead perhaps being related more to puberty-independent developmental processes. Thus, even in a simple animal model where one might expect behavior to be more straightforwardly driven by hormones than in human adolescents, evidence for organizational effects of pubertal hormones thus far appears to be primarily related to reproductive and other strongly sexually-dimorphic behaviors, with other adolescent-typical behaviors and their post-adolescent decline associated with puberty-independent maturational processes. These differences could potentially reflect differences in the evolutionary function of these behaviors. For instance, it could be speculated that early adolescent rises in the reward value of novelty, social stimuli and other rewarding stimuli (including alcohol and other drugs) may have been evolutionarily conserved to encourage novelty-seeking and facilitate emigration of the organism away from its family unit prior to sexual maturation, thereby avoiding inbreeding and its deleterious effects (e.g., see Spear, 2004). Multiple approaches using converging evidence obtained from both basic science studies and research with human adolescents will be necessary to dissect these dynamic interrelationships between neural, hormonal and behavioral changes during adolescence.

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- Gonadectomy exerted only modest effects on ethanol responsivity.
- Ontogenetic decline in ethanol intake in males is partly under control of androgens.
- Pre-pubertal sham surgery robustly altered ethanol intake and sensitivity.

Table 1

Ethanol intake: Impact of pre- and post-pubertal gonadectomy (summary of main results from Vetter-O'Hagen & Spear, 2011b).

Gonadectomy	Sex	Ethanol intake during adolescence	Ethanol Intake during adulthood
Pre-pubertal on postnatal day (P) 23	male	**No changes** relative to sham and non-manipulated controls	**Increased** relative to sham and non-manipulated controls
	female	**No changes** relative to sham and non-manipulated controls	**No changes** relative to sham and non-manipulated controls
Post-pubertal on P70	male	N/A	**Increased** relative to sham and non-manipulated controls
	female	N/A	**No changes** relative to sham and non-manipulated controls

Table 2

Impact of surgical manipulations (sham control) on ethanol intake and sensitivity, social motivation and novelty-directed behavior (summary of major findings from Vetter-O'Hagen & Spear, 2011b; Vetter-O'Hagen & Spear, 2012).

Age of sham surgery	Sex	Adult ethanol intake (Vetter-O'Hagen & Spear, 2011b)	Adult ethanol sensitivity (Vetter-O'Hagen & Spear, 2012)	Adult social preference (Vetter-O'Hagen & Spear, 2012)	Adult Novelty-directed behavior (Vetter-O'Hagen & Spear, 2012)
P23	male	**Increased** relative to non-manipulated controls	**Eliminated** ethanol-induced decreases in social preference seen in non-manipulated and gonadectomized males and females	**Decreased** relative to non-manipulated and gonadectomized males and females	**Decreased** relative to late (P70) sham male and female controls
	female	**No changes** relative to non-manipulated controls			
P70	male	**No changes** relative to non-manipulated controls	**No changes** relative to non-manipulated controls	**No changes** relative to non-manipulated controls	**No changes** relative to non-manipulated controls
	female				