

WORKSHOP ON THE SYNTHESIS OF RESEARCH ON ADOLESCENT HEALTH AND DEVELOPMENT

Neuroendocrine and Neural Contributions to Pubertal Development, Normative Adolescent Development and Affect-Related Behavior Problems

Background Paper Prepared by

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1. Introduction and Overview and Brief Digressions

This review will provide background literature about the influence of pubertal hormones on emotion and motivation in adolescence, with particular attention given to our knowledge about the variance in hormonal measures in selected adolescent populations. I have chosen to focus on peripheral biological changes that cause puberty and those that result from pubertal maturation in order to gain a better understanding about how biological events can impact adolescents' social and emotional development in relation to situational factors and processes. This may, in turn, lead to a better understanding of how some biological changes in pubertal individuals can contribute to the emergence of problem behavior. This review will be developmental since the organizational-activational hypothesis implicates critical periods across the full range of development. Some of these effects may implicate hormone levels, but this cannot be the whole story. A developmental framework implicates the importance of timing and synchrony (Dahl, 2004).

Adolescence can be defined as *that awkward period between sexual maturation and the attainment of adult roles and responsibilities* (Dahl, 2004). The first part of adolescence, marked by pubertal development and the activation of neuroendocrine systems will be the focus of this review for personal and conceptual reasons. At the tender age of eighteen, when I was an adolescent myself, my personal interest in how hormones interface with the social context of youth was fostered by my senior honors thesis. This area of research resonates with me for conceptual reasons. The literature on hormones is daunting because it is scattered across every conceivable hormone-behavior relationship: null results are the rule rather than the exception. It seems inconceivable that a steroid should have so much and so little impact on adolescent behavior. Yet, our understanding of the biology of hormones places them at the center of the intersection between our genes and environments (Gottlieb, 1991). Hormones are the scaffolding for the genetic blueprint of the individual; over seconds, minutes, hours and days, they activate genes nearly everywhere in the human body. Genes are unchanging, but hormones allow their expression to vary across time, social contexts, physical environments and developmental stages (Gottlieb, 1996).

Hormones are remarkably responsive to the environment. These steroids change drastically in response to our physical, social and emotional environment. These are *activational effects*, when concurrent hormone levels activate gene expression to influence our propensities for particular behaviors. Often, these activational effects relate to metabolism and energy stores. But hormonal influences on the genetic blueprint can persist for long periods of time, perhaps indefinitely. Phoenix, Goy and Young (1967) proposed the *organizational-activational hypothesis* to explain the observation that the same hormones that organize the body and the brain in fetal and early postnatal life will later exert activational effects after puberty (see Romeo, 2003 for a more recent review). These *organizational effects* are testaments to the powerful regulatory role that hormonal exposure during critical early periods can exert across the entire lifespan on the individual. This model (Rubin, Reinisch, & Haskett, 1981), in combination with models for fetal programming (Plant & Barker-Gibb, 2004), suggest that hormones

come on the scene in fetal and early postnatal life to organize the body and the brain. These early signals allow the intrauterine environment to predict what the individual's future will hold. Some organizational influences may not change hormone levels, *per se*, but will change the timing at which hormonal signals begin to activate secondary sexual characteristics. Hormonal interactions with the developing individual's genetic blueprint will then permanently alter how that person will interface with their future social and physical environment.

And yet, for most of childhood, juveniles experience a period of hormonal quiescence after organizational forces diminish. Nevertheless, children respond to their social and physical environments, so something more than hormonal cues can change our genetic structure. Organizational effects allow the individual the ability to predict their future environments, but the active inhibition of hormones during childhood *permits* childhood, thus affording distinct advantages of delayed sexual maturity and opportunities for additional neural development (Bjorklund, 1997). I will also review other biological changes in adolescence, and I will highlight when concurrent hormones are not likely implicated.

Before launching into the biology of puberty, a brief note about the policy implications of biology is warranted. A colleague of mine, Sheri Berenbaum, once asked about the utility of including hormonal measures in research if its explanatory power is redundant with a psychological questionnaire. Such a view is common in psychology, though the pendulum may have swung so far as to suggest that self-reported measures are invalid because humans, especially children, are so poor at introspection (Davidson, 2003). There are at least three possible policy oriented reasons for exploring biological contributions to pubertal maturation: (1) biologically informed methods may indicate a mechanism or provide a window into the etiology of a disorder or developmental phenomena. This may particularly be true when we consider the interplay between biological and social forces (e.g., Hankin & Abramson, 1999; Raine, 2002); (2) Biological forces may indicate who is the most vulnerable to a particular disorder (e.g., Moffitt, 1993) or, more interestingly, in what biological state an underlying vulnerability is most likely to be expressed; (3) intervention research that indicate an initial biological vulnerability may be able to demonstrate changes in this objective biological outcome measure in longitudinal studies (e.g., Fisher, Gunnar, Chamberlain, & Reid, 2000).

The general organization of this review will be to start at central events in the brain that trigger the onset of puberty, and then work out through the hypothalamic-pituitary-gonadal (HPG) axis to the gonadal steroids in the periphery. Gonadal steroids cause secondary sex characteristics, immortalized by the Tanner stages, so these physical changes and the timing of these changes are included in the next section. Next, there will be some digression back into the brain since steroid hormones are notorious for feedback loops that influence a wide variety of brain structures and neurotransmitter systems. Because the brain is a major interface with our behavioral control, it has a natural progression to discussions of behavioral changes evident in adolescents including mood and affective disorders.

The take-home message is that a direct relationship between hormones and behavior is unlikely, especially since it takes so long for hormones to be released

and even longer for them to exert an effect on genetic expression (Susman, 1997). Nevertheless, hormonal changes are central to our understanding of the interface between our genes and our environment. Adolescents have been described as victims of *Raging Hormones* and adolescence as a period of *Storm and Strife* for one hundred years. Study after study begins with such statements, then quickly dismiss the model after examining a simple hormone-behavior relationship. Raging Hormones have become cliché: an overly simplistic model is explored; null results are obtained; the idea that hormone-behavior relationships in adolescents exist are easily dismissed (Buchanan, Eccles, & Becker, 1992). This is ironic because endocrinologists have long known that hormones rarely cause a behavior but rather exaggerate one's propensity for that behavior if it is already expressed (Sapolsky, 1997). Raging Hormones have become a *straw man* argument for biological changes in adolescents before the nature of those biological changes in relation to adolescent behavior problems have been sufficiently empirically explored. Dismissing the role of hormones in adolescent behavior has been premature because sufficient attention has not been paid to understanding the nature of the systems before embarking on a fishing expedition. This review will emphasize when a type of hormonal effect – status, level, rate, salience, synchrony, timing, – appears most fruitful based on our current understanding of pubertal development (Brooks-Gunn & Warren, 1985).

2. Causes of Pubertal Maturation Necessitates a Brief Biology Review

In contrast to the popular view that puberty is marked by the advent of new abilities or functions, current hypotheses emphasize that the juvenile period is characterized by active inhibition of adult-like physiological profiles, organized *in utero* and during early postnatal development, which are actively suppressed during childhood. The cause of the brake release is unknown, but elegant animal models have been described by several independent research laboratories. These research lines converge on the idea that puberty is initiated in the brain (rather than the gonads) when there is a reduction in inhibition and an increase in excitation at the hypothalamic level of the HPG axis. That the initiation of puberty begins in the brain is underscored by the observation that positive and negative feedback effects of gonadal steroids on the hypothalamus, essential for sexual maturation and cyclic hormonal changes in adults, is not effective in the pre-pubertal animal (Terasawa & Fernandez, 2001). Nevertheless, it is interesting that some of the pubertal triggers, though steroid-independent in the pubertal animal were, in part, organized by gonadal steroids. The idea that puberty is caused by steroid-dependent and steroid-independent events must be merged with the organizational-activational hypothesis and our knowledge that some developmental effects of gonadal steroids may be protracted. Puberty ensues when sufficient input causes the GnRH pulse generator to be activated. This section reviews animal models of the mechanism for pubertal onset and the re-activation of the GnRH pulse generator.

2.1] The GnRH pulse generator is a Central Marker for Pubertal Onset

The GnRH pulse generator refers to the intermittent discharge of GnRH (alternately termed LHRH) from the hypothalamus into the hypophysial portal

circulation, marking the first stage of the hypothalamic-pituitary-gonadal (HPG) axis (Plant, 2001b). Few neurons in the brain synthesize GnRH, whose primary role is to stimulate the synthesis and release of FSH and LH from the anterior pituitary (Jennes & Conn, 2002). The addition of the ‘pulse generator’ terms emphasize that GnRH is released occasionally in juveniles, but bursts of GnRH release must be frequent, of high amplitude, and regularly timed for pubertal maturation to occur. Interruption of pulsatile GnRH release in the adult leads to hypogonadism, a finding that demonstrates the importance of the GnRH pulse generator in sexual maturation (Plant & Shahab, 2002). The awakening of the GnRH pulse generator has become synonymous with the developmental clock that triggers puberty, so an accumulating body of animal research has been designed to uncover the mechanism for GnRH pulse generator activation.

An increase in episodic GnRH secretion is activated by a host of signals, primarily at the hypothalamic level, which involve a decrease in inhibitory signals, an increase in excitatory signals, and a wide variety of permissive factors contributing to the onset and progression of puberty. A review of biological and environmental factors which influence pubertal timing will contribute to our understanding of mood and mood disorders because many of the factors which influence puberty likewise exert direct or indirect effects on psychopathology. GABA and glutamate are two of the main neurotransmitters which influence the activation of the GnRH pulse generator.

2.2] Oh, “G”: A Three Part Model for Pubertal Onset Involves GABA, Glutamate and Glia

GABA is an inhibitory neurotransmitter with implications for psychopathology treatment and intervention (see review by Petty, 1995). GABA provides the chief inhibitory neuronal input agent restraining GnRH release. GABA has receptors located nearly everywhere in the brain but notably in sexually dimorphic brain areas, including the hypothalamus (McCarthy, Auger, & Perrot-Sinal, 2002). In adults, GABA is regulated by and helps to regulate the HPG axis (McCarthy et al., 2002). Early in fetal development, GABA is actually excitatory, and is centrally involved in sexual dimorphisms of the developing brain during this window of excitation (Owens & Kriegstein, 2002). As fetal development continues, and through activation by organizational influences of gonadal steroids like testosterone, however, GABA gradually becomes largely inhibitory in the developing brain (McCarthy, Davis, & Mong, 1997). In the juvenile state, GABA exerts a strong inhibitory effect on GnRH release and on glutamate’s ability to stimulate GnRH release. At the onset of puberty, however, GABA’s inhibitory control over GnRH and glutamate release diminishes, allowing GnRH release to occur more frequently as well as permitting glutamate neurons to stimulate GnRH release. Thus, GABA directly and indirectly inhibits the GnRH pulse generator in the juvenile which diminishes during the pubertal stage of development. In pubertal and postpubertal individuals, GABA’s release is influenced by gonadal steroids, though these signals are not active in juveniles (Styne & Grumbach, 2002). This decline in GABA activity in the hypothalamus is the first known signal marking the advent of pubertal maturation; it is not currently known what causes this decline in the efficacy of

GABA's control over the GnRH pulse generator, although several genes have been postulated (Ojeda & Terasawa, 2002). One final note about the role of GABA in the maturation of the GnRH pulse generator is that the supporting evidence for GABA in the onset of puberty is stronger in female than male monkeys. This does not invalidate the model for males, but rather raises the possibility that sex differences in GABA, organized prenatally by testosterone, may persist through the juvenile pause and re-emerge near the onset of puberty.

The main excitatory neurotransmitter controlling the GnRH pulse generator is glutamate through NMDA and kainate receptors that directly stimulate GnRH pulses from hypothalamic neurons. Glutamate has been implicated in forms of psychopathology such as Schizophrenia, Posttraumatic Stress Disorder, and anxiety (Bergink, van Megen, & Westenberg, 2004; Chambers et al., 1999; Chang, Alsagoff, Ong, & Sim, 1998; Schiffer, 2002) and is a key component of Sapolsky's model of neurotoxicity and mechanisms of neuron death (Sapolsky, 1990; Sapolsky, 1992). Early in fetal development around the same developmental window as GABA (Sims & Robinson, 1999), sex steroids up-regulate glutamate. Glutamate's role is distinct from GABA by remaining excitatory in both males and females (Grumbach, 2002), but the male brain is nonetheless exposed to more neuronal excitation as a result of both GABA and glutamate (McCarthy et al., 1997). Factors which cause glutamate neurons to increase their direct control of GnRH release near the onset of puberty are currently unknown, although, interestingly, the availability of glutamate in the synaptic cleft is partially determined by GABA. GABA is synthesized from glutamate (via GAD enzymes), and these enzymes which control the biosynthesis of GABA and glutamate change at the time of puberty. This suggests that the increase in glutamate during pubertal maturation may be secondary to the decrease in inhibitory GABA activity, and that the bioavailability of both of these neurotransmitters is dependent on one another (Terasawa et al., 2001). Interestingly, a component of glutamate input through NMDA receptors is inhibitory to GnRH release in juveniles, and then gradually becomes stimulatory to GnRH near the onset of puberty. By the end of puberty, glutamate is nearly entirely excitatory for the GnRH pulse generator (Terasawa & Fernandez, 2001). Thus, glutamate directly influences the maturation of the GnRH pulse generator, in part, through reductions in the quantity of glutamate that is converted to GABA, and also, in part, because GABA neurons exert less of an inhibitory effect on glutamate excitation.

The third pubertal trigger involves astroglial cells regulating the secretion of GnRH neurons (Ma & Ojeda, 1997). Like neurons, astroglial cells generate and convey information within the nervous system. Astroglial cells in the hypothalamus primarily communicate via local or nearby release of growth factors and neurotransmitters or their precursors (Ojeda & Terasawa, 2002). Glial-to-neuron contact is abundant in early pubertal monkeys when serum estrogen levels are low, but such extensive connections are not present during later life stages (Grumbach, 2002). This suggests that glial-to-neuron communication is maximized at pubertal onset. That is, changes in glial-to-neuron contact will be most plastic during pubertal onset, but will later become more entrenched when gonadal steroids primarily regulate the GnRH pulse generator (Ojeda & Ma, 1999). Glial cells function primarily during the critical window of early pubertal maturation by

producing several growth factors, including IGF-I, basic fibroblast growth factor, TGF α and NRG (Ojeda & Terasawa, 2002).

IGF-I acts directly on the hypothalamus to increase the activity of GnRH pulse generator. IGF-I is secreted as a growth factor by glial cells and a substantial portion is also of peripheral origin (Terasawa et al., 2001), raising a possible partial pathway for a pubertal signal or trigger to originate in the body rather than centrally in the brain. Basic fibroblast growth factor is another growth factor released by glial cells which directly stimulates GnRH release, stimulates the release of GnRH precursors, and contributes to the proliferation of neighboring glial and neuronal cells (Ojeda & Terasawa, 2002).

Two epidermal growth factors, TGF α and NRG contribute indirectly toward the initiation of puberty, particularly for females, through juxtacrine (i.e., cell-to-cell) communication (Terasawa et al., 2001). These growth factors do not directly interact with GnRH neurons, but rather these growth factors bind to glial cell receptors that are adjacent to GnRH neurons which then stimulate the release of prostaglandin E₂ and glutamate. It is prostaglandin E₂ which then directly stimulates the GnRH pulse generator. The expression of mRNA for these growth factors is low in juvenile animals, and then is maximized at the time of puberty, notably on the day of the first preovulatory surge of gonadotropins. Later, these growth factors will be regulated by gonadal steroids though this first surge is steroid-independent (Plant, 2001b). This is suggestive of an important developmental window for juxtacrine interactions with glial cells in maturing hypothalamic tissue. One interesting note about Ojeda and Terasawa's pathway (2001) is that astroglial cells will indirectly cause the release of prostaglandin E₂ and glutamate in order to stimulate the GnRH pulse generator; and astroglial cells themselves are regulated by glutamate neurons. This suggests that glutamate will directly and indirectly act upon GnRH neurons through neuronal and glial cellular communication (Ma & Ojeda, 1997). This may be one reciprocal pathway through which pubertal triggers greatly amplify the GnRH pulse generator signal in the hypothalamus.

2.3] Permissive Pubertal Factors May Accelerate Maturation Rates

As puberty progresses, other neurotransmitters systems participate in the control of GnRH release (Terasawa & Fernandez, 2001). Positive and negative feedback mechanisms of gonadal steroids, notably estrogen, exert their effect primarily after the onset of puberty at multiple levels of the HPG axis, with receptors located on glutamate, GABA and GnRH neurons (Terasawa & Fernandez, 2001). These other neurotransmitters and neural substances have been postulated to be the pubertal trigger, but their effects temporally proceed from the developmental changes in GABA, glutamate and glial cells. Thus, neuropeptide Y (NPY), norepinephrine, dopamine, serotonin, endogenous opioids, leptin and melatonin are considered permissive factors which contribute to the progression of puberty and which may be necessary for puberty to continue, but which are not sufficient stimulators of the GnRH pulse generator (Sisk & Foster, 2004). Because permissive factors take effect after the initial maturation of the GnRH pulse generator, they are

frequently steroid-dependent factors (Sisk & Foster, 2004) and are the likeliest candidates for important environmental modulation of pubertal maturation rates.

Neuropeptide Y (NPY) is a major component of the juvenile brake on the GnRH pulse generator in some models (Plant, 2001b), but is more tentatively permissive in others (Terasawa & Fernandez, 2001). Plant (2002) considered NPY as a pubertal trigger of the GnRH pulse generator when he observed a decrease in NPY gene expression in the hypothalamus during the juvenile to pubertal transition (see also Sutton, Mitsugi, Plotsky, & Sarkar, 1988). Terasawa and Fernandez's (2001) model, however, emphasizes the developmental shift in NPY's function as an individual progresses from the juvenile to postpubertal state. NPY primarily inhibits GnRH activity in juvenile animals indirectly by inhibiting glutamate activity in the hypothalamus (Plant, 2001b). This inhibitory signal disappears near the onset of puberty, or is inconsistently shown to be inhibitory or excitatory. In post-pubertal animals, NPY activity is modulated by leptin and estrogen; NPY is inhibitory when estrogen levels are low and then estrogen facilitates NPY action particularly in adults, acting mainly indirectly through glutamate neurons (Terasawa & Fernandez, 2001).

Other neurotransmitters, which have been repeatedly connected to mood disorders, help regulate the GnRH pulse generator and maturation rates in pubertal animals (Stomati et al., 2000). Norepinephrine appears centrally important for the onset of puberty in rodents, but is a permissive factor in primates (Plant, 2001a). Norepinephrine levels are low in prepubertal individuals and then drastically increase by midpuberty. This sharp rise in norepinephrine then contributes to the increase in GnRH release during pubertal development. Norepinephrine may be especially important toward the end of pubertal development as it does not alter the timing of menarche, but it does advance the age of first ovulation, one of the last signals of pubertal development in the female (Terasawa & Fernandez, 2001). Norepinephrine is partially regulated by prostaglandins and estrogen in pubertal animals and is thus becomes a component of steroid-dependent GnRH pulse generation (Sisk & Foster, 2004).

Other catecholamines, such as dopamine, also control the release of GnRH. Dopamine both stimulates and inhibits GnRH release, though the timing of this innervation in relation to the onset of puberty has not yet been established in pubertal animals (Terasawa & Fernandez, 2001). Serotonin is connected to pubertal maturation in that elevations of serotonin in the hypothalamus contributes to precocious puberty and reduced serotonin concentrations contribute to delayed puberty. The direction of the effect of serotonin on the HPG axis is dependent on developmental timing and the gonadal state of the individual, suggesting that the permissive effects of serotonin depend on interactions with estrogen and testosterone in a classic steroid-dependent manner (Terasawa & Fernandez, 2001).

Endogenous opioids are frequently implicated in positive mood, affect, and social bonding in part because they have dense receptors in reward and emotion circuitry in the brain (Keverne, 2004). Endogenous opioids are also implicated in sex differences in the female response to stress, particularly when moderated by estrogen (Taylor et al., 2000). Opioids actively suppress the HPG axis, so they were

a candidate for a pubertal trigger (Mena-Valdivia, Nava-Espinosa, & Malacara-Hernandez, 1995). However, opioid antagonists do not increase the activity of the HPG axis until after the onset of puberty (Ojeda & Terasawa, 2002). The effectiveness of these antagonists increases throughout pubertal maturation, in part because opioid activity is highly activated by estrogen. Thus, endogenous opioids inhibit glutamate's ability to stimulate GnRH release in mature individuals, but not before pubertal onset, especially when estrogen levels are high (Terasawa & Fernandez, 2001). Opioids are a good candidate for the regulation of sexual maturation in relation to environmental events rather than acting as a pubertal trigger (Jenkins & Grossman, 1993; Stomati et al., 2000).

Leptin is an important hormone related to satiety, appetite suppression, and energy expenditure (Cacioppo et al., 2002). Although early evidence indicated that rising leptin levels were observable before other signals of pubertal maturation (i.e., increased gonadal steroids) and that mutation in the genes encoding leptin resulted in delayed or absent pubertal development in boys or girls (Plant, 2001a), most investigating laboratories have rejected the idea that leptin serves as the pubertal trigger (Ojeda & Terasawa, 2002). Leptin does not act directly on the GnRH pulse generator (Styne & Grumbach, 2002), but rather exerts an effect after pubertal onset indirectly through NPY. Leptin may augment the NPY pubertal signal since NPY neurons have leptin receptors (Plant & Shahab, 2002). Given that NPY's main role in the GnRH pulse generator is after the onset of puberty, it seems likely that leptin's permissive role is heralded rather late in pubertal development. Indeed, peak concentrations of leptin in girls is at Tanner stage 5 (Styne & Grumbach, 2002). It is also interesting that prepubertal and early pubertal leptin levels correlate more with body mass index and age than with pubertal maturation (Styne & Grumbach, 2002). It is possible that the purpose of leptin as a permissive factor is to serve as a marker of peripheral physical development (Plant & Shahab, 2002). When sufficient weight and growth has been attained for sexual maturation, leptin may permit physical development to continue. If there is a fall in circulating leptin below a critical level, delayed sexual maturation may result (Grumbach, 2002).

The implication that melatonin causes the onset of puberty is derived largely from the observation that the GnRH pulse generator is re-awakened at night (Styne & Grumbach, 2002) and that blind boys have delayed puberty (although blind girls have earlier menarche than normal girls) (Terasawa & Fernandez, 2001). Melatonin levels are elevated in early childhood, decline during late childhood and remain stable from early puberty through adulthood (Vessely & Lewy, 2002). This profile suggests that melatonin may have an inhibitory role as a restraint against the initiation of puberty (Ojeda & Terasawa, 2002). However, the GnRH pulse generator is activated approximately two months earlier than the decrease in nocturnal melatonin and treatment with melatonin does not delay puberty (Ojeda & Terasawa, 2002). The observation of blind boys and girls having off-timed puberty hints toward the involvement of the suprachiasmatic nucleus of the hypothalamus upstream of the release of melatonin. Although the mechanism that links the suprachiasmatic circadian clock with the developmental clock is unknown, glutamate has been implicated as the primary neurotransmitter mediating light/dark signaling (Ojeda & Terasawa, 2002). Thus, melatonin may be an effect of

the GnRH pulse generator activity instead of a trigger of pubertal onset or it may be operating as a signal for some upstream interactions within the hypothalamus.

2.4] Summary and Integration

The onset of puberty occurs in the brain, not the gonads. The hypothalamus releases intermittent pulses of GnRH during the juvenile pause, and these pulses become more frequent and robust as puberty ensues. The control of the GnRH pulse generator is primarily through a decrease of inhibitory signals from GABA, an increase of excitatory signals from glutamate, and juxtacrine astroglial-to-neuron communication via several growth factors and the release of prostaglandin E₂ and glutamate within the hypothalamus. These events are steroid independent at pubertal onset, but may interact with sex steroids once puberty has begun. If the dichotomy between steroid-dependent and -independent events is to be believed, then research aimed at understanding concurrent neuroendocrine interactions with mood and affect may best be applied after the maturation of the GnRH pulse generator has begun. Several neurotransmitters and hormones also serve a permissive role as a contributing factor toward the progression of puberty. Many of these signals are steroid dependent and interact heavily with other hormones, neurotransmitters, or environmental triggers. This model emphasizes that the organization of the juvenile, pubertal and post-pubertal brain is enormously different, with reversals in function and directionality occasionally evident across neurotransmitter systems. The regulation of the juvenile brain may primarily be influenced by central events, whereas the maturation of the GnRH pulse generator in the adolescent opens a wider window for opportunities for interactions with peripheral measures such as steroid hormones and, in turn, environmental events. This perspective dovetails nicely with the model for adolescent brain development proposed by Dahl (2004) in which some brain areas (i.e., the limbic system and the hypothalamus) are relatively steroid-dependent (or at least influenced by steroid hormones), whereas other brain areas (i.e., the prefrontal cortex) are steroid-independent. The current model also emphasizes the disjunction in the timing of steroid-dependent and -independent events. The main implication of this idea is that the same intervention applied to a pre- or mid- or post-pubertal individual will not have the same effect on that individual's biology or likely behavior.

A brief digression illustrates this latter point. During my graduate education in Biobehavioral Health I lived in a poor small town in Pennsylvania. My next door neighbor was a fecund woman with six children, one of whom was a six year old girl with juvenile onset diabetes. Her disease was poorly controlled as ambulances regularly appeared outside our door. One of my professors, Jan Ulbrecht - an expert in diabetes - considered diabetes to be the perfect biobehavioral disease because negative biological effects can be maintained through adequate behavioral control. I asked him about my neighbor, concerned that this little girl would soon be losing toes or going blind. He replied that the interesting thing about diabetes is that none of the negative repercussions of the disease set in until puberty. A child can poorly maintain their diabetes and be fine. As soon as puberty hits, however, they will start experiencing lifelong complications. He recommended waiting until the girl was old enough to understand her own disease to intervene, focusing on

training the girl rather than her negligent parents. This digression illustrates the point that our biology, particularly our hormones, behaves fundamentally differently in juveniles and adolescents. Our model for behavior, disease, and intervention cannot assume that the basic biology of individuals at these life stages is similar.

3. Environmental Triggers Suggest Plasticity in Pubertal Maturation Rates

The above review focuses on events that contribute to the initiation of pubertal onset. Little attention is paid to the timing of events unless pubertal delays or precocious puberty signal the involvement of a neurotransmitter or neural substance. However, the timing of puberty, when the cascade of pubertal events begins, involves a host of environmental factors such as nutrition and weight, family conflict and composition, genetic and familial transmission, social rank, birth weight, adoption status, and environmental estrogens. Because the initial cascade that reawakens the GnRH pulse generator is largely steroid independent, it is likely that these environmental factors exert their effects primarily by accelerating pubertal maturation once central events have been initiated (Sisk & Foster, 2004). That is, given that steroid hormones are proposed to be the primary pathway through which environmental factors influence pubertal maturation and that steroids influence the GnRH pulse generator after the initial onset of puberty, the role of the environment in triggering pubertal onset is most likely secondary to the initial genetic and neural control of pubertal onset.

3.1] Race

In boys in the United States, the mean age of onset of puberty is 11 years, with a range from 9 to 13.5 years. Consistently, the mean age of onset for girls is younger and more variable. The mean age of onset for girls in the United States is 10.6 years with a range from 6.7 to 13 years (Styne & Grumbach, 2002). It should be noted, however, that these estimates do not generalize across race or country. For example, African Americans have a consistently earlier pubertal onset and Mexican American boys have a later onset than white boys. Presumably the timing of puberty across races relates to cultural differences in nutrition and food availability. It is interesting, then, that rural children in South America and Africa have better nutrition and have earlier puberty, though there is an opposite pattern of ruralness in the United States (Styne & Grumbach, 2002). The interplay between pubertal timing, race, and cultural forces seems far from conclusive. Rather than focus on racial differences, most of the literature has attempted to understand the nutritional influences on pubertal maturation as a causal mechanism explaining the link between race and pubertal timing.

3.2] Nutrition, Weight, and Exercise Postpone or Accelerate Puberty

The notion that nutrition or health may be the mechanism for accelerated pubertal timing came from historical records which indicated that puberty in the United States (and subsequently other developing countries as well) used to occur later. The average age of menarche decreased approximately 2 to 3 months per decade since the 1900s, though little evidence indicates a continued trend past the 1950s (Styne & Grumbach, 2002). The reason for pubertal maturation to be linked

to nutrition and body fat may be evolutionary. The timing of puberty is at least in part stimulated by some metabolic signal, presumably leptin, that tells the brain that the body has enough metabolic stores and is big enough to support reproductive function (Cameron, 1991).

Beginning in the 1970s, Frisch pioneered the idea that there is a critical amount of fat necessary for pubertal advancement, menarche and first ovulation (Frisch, 1984, , 1993, , 1996). Indeed, there appeared to be a particular ratio of fat to lean mass which was necessary for pubertal onset and the maintenance of female reproductive ability in animals and humans (Frisch, 1980). Interestingly, high levels of exercise delays pubertal development, especially in sports that require a lean body mass (e.g., ballet dancers). Cessation of exercise or training for as little as two months prompts menarche and advanced breast development (Graber & Brooks-Gunn, 1995). The importance of the 'critical weight' idea was further strengthened by the observation that adults who fell below that critical ratio stopped menstruating and reverted to pre-pubertal like pulses of GnRH. For example, women who diet excessively do not have menstrual cycles, and less strenuous exercise or weight loss results in anovulatory cycles or a shortened luteal phase (Frisch, 1987). The discovery of leptin several years later provided a mechanism to explain how signalling for weight, hunger, and fat ratios could be incorporated as a permissive factor for the maturation of the GnRH pulse generator (Cacioppo et al., 2002). The connection between body fat and pubertal maturation must be reciprocal, however, since one of the hallmarks of pubertal maturation (in females especially) is increasing fat deposits.

The 'critical weight' hypothesis raised the question of whether greater ratios of fat to lean body mass would contribute to advancing pubertal onset. This led to much speculation of leptin as the pubertal trigger, an idea which has been rejected (Plant, 2001a). Nevertheless, in humans, weight is inversely correlated with age of menarche even after controlling for age (Graber & Brooks-Gunn, 1995), and several family measures (Moffitt, Caspi, Belsky, & Silva, 1992), and moderately obese girls have an earlier age of menarche (Styne & Grumbach, 2002). Primate studies also indicate that females with an earlier age of first ovulation had higher body mass indexes (Wallen & Zehr) and faster postnatal growth (Coe & Shirtcliff, 2004), suggestive of better nutritional reserves. It must be noted, however, that age of menarche or age at first ovulation are rather late developmental markers for pubertal maturation. Though heavier girls may enter puberty at the same time based on central events (i.e., the GnRH pulse generator is not influenced by BMI), leptin, weight, and other markers of nutrition may permit them to advance more quickly through pubertal stages.

The observation that nutrition and puberty are concurrently interrelated raised questions about the duration of the effect. Studies in primates, for example, indicate that skipping a single meal impairs the activity of the HPA axis (Cameron, 1996). In humans, fasting for a single day suppresses LH levels, with measurable declines in LH within four hours of missing a single meal (Cameron, Helmreich, & Schreihofner, 1993). This may indicate that the connection between nutrition, weight and puberty is robust or that it is transient. Some longitudinal evidence exists to

support the former. Girls who weigh more at age 7 had earlier menarche (Cooper, Kuh, Egger, Wadsworth, & Barker, 1996), and girls who weigh more as early as age 5 go into early puberty (Davison & Susman, 2001). The impact of nutrition and body weight, then, has been extended downward to developmental stages that clearly precede first signs of puberty (Cole, Martin, & Dennis, 2004).

3.3] Low Birthweight Paradoxically Associated with Early Puberty

A growing body of literature demonstrates that the effect of weight and growth includes the full range of growth, even fetal growth and birthweight. The direction of this effect is counterintuitive, however, suggestive of a ‘fetal programming’ effect originally hypothesized by Barker (2004). For example, Ibanez and colleagues (1999; 2000; 1998; 1999) have shown consistently that girls with precocious puberty are likely to have been born small for gestation age or with frank intrauterine growth retardation. Similarly, several research groups have shown that, compared to girls with normal or high birthweight, girls born small for gestational age (Koziel & Jankowska, 2002; Persson et al., 1999) or with lower birthweight within the normal range have an earlier onset of puberty (Delemarre-van de Waal, van Coeverden, & Engelbregt, 2002). The effect of fetal growth on the timing of puberty does not appear to be mediated through premature birth (Persson et al., 1999). Interestingly, alterations in pubertal timing occur as a result of faster progressions through puberty rather than showing earlier initial signs of pubertal activation. Normal birthweight girls are protected from early maturation difficulties by progressing more slowly through the pubertal transition (Ibanez et al., 2000).

The fetal programming hypothesis can reconcile the finding that low birthweight and heavier childhood weight contribute to advanced pubertal age. The idea is that when intrauterine growth is stunted or slowed, the individual is programmed for fewer nutritional resources in postnatal life. The endocrine axes are especially affected by this early signal. However, when nutritional resources are instead abundant, there is a mismatch between the environment that the individual is prepared to encounter and the environment they are exposed to. The fetal programming hypothesis emphasizes that differences between fetal and postnatal growth may contribute to altered developmental trajectories (dos Santos Silva et al., 2002). In support, it is only when low birth weight girls show “catch-up” growth do they evince early puberty (Adair, 2001; Ong, Preece, Emmett, Ahmed, & Dunger, 2002; Strong & Dabbs, 2000). One important effect of this early growth acceleration is that low birthweight girls may catch up in weight, but they do not often catch up in their final adult height (Ibanez et al., 2000), in part because of earlier pubertal maturation. Indeed, 20% of low birthweight girls are overweight at 15% are obese in early adulthood (Walkup et al., 2003).

3.4] Family Context and Child Rearing Practices in Early Childhood may Advance Puberty

Belsky, Steinberg and Draper (1991) provide an evolutionary framework for the observation that early social and contextual forces may change the timing of puberty. This model is intriguing because it focuses on the impact of social resources, rather than the more obvious nutritional resources for advancing

puberty. They outline two distinct pathways for reproductive strategies which are developmentally organized in early postnatal life. The 'Opportunistic' strategy is characterized by marital discord, inadequate financial resources and high family stress. Parents in this strategy treat their children in a harsh and rejecting manner and their children, in turn, frequently develop insecure attachment and a mistrust of caregivers and close family members. In boys, this pathway leads to aggressive and noncompliant behavior, which may later develop into externalizing behavior problems. In girls, this leads to internalizing behavior problems, anxiety, and depression. Each component of the early social environment contributes to earlier pubertal maturation. The outcome of this model (namely, precocious sexual behavior) will be discussed below. The other strategy is characterized by adequate financial and familial resources, warm and responsive caregivers, and secure attachment. These environmental forces promote later physical maturation, delayed sexual activity, and greater parental investment.

This model has received some empirical support (Kimonides, Khatibi, Svendsen, Sofroniew, & Herbert, 1998; Moffitt et al., 1992; Wierson, Long, & Forehand, 1993), although there has been some contradictory evidence (Campbell & Udry, 1995) or modifications. For example, early pubertal timing was related to dyadic stress between mothers and daughters and biological father absence, but the latter effect was accounted for by stepfather presence rather than biological father absence (Ellis & Garber, 2000). This suggests the possibility for pheromonal explanatory mechanisms (McClintock, 1998). Another study found that fathers' presence, more time spent with fathers, greater parental support and affection predicted later pubertal timing, suggesting that it is the positive dimension of family relationships, rather than the 'opportunistic pathway' which accounted for delayed pubertal maturation (Ellis, McFadyen-Ketchum, Dodge, Pettit, & Bates, 1999). Also, Graber and Brooks-Gunn (1995) provided support for Belsky's (1991) model, with the addition that number of life events were unrelated to pubertal timing, so it appears that there is something unique to the family context in prediction of pubertal maturation. In sum, the family context serves as a social environmental factor in early childhood to signal two optimal developmental pathways. This model dovetails nicely with fetal programming effects by extending the critical window into early social programming. It also highlights models for the intergenerational transmission of risk (Elder, 1996) and the potential benefit of including biologically informed measures into explanations for such social processes.

3.5] Family Context Confounds Genetic Influence on Pubertal Maturation

The biggest confound with Belsky's (1991) model is not related to its empirical support, as much as the argument that a shared heritable characteristic may be a more parsimonious explanation for early puberty in conflictual families (Kimonides et al., 1998; Moffitt et al., 1992). The genes that influence family context may likewise travel with the gene(s) that govern the onset of puberty and the GnRH pulse generator. Alternatively, characteristics in the mother which advance her pubertal maturation may similarly advance her daughter's maturation trajectory. These factors are not necessarily of genetic origin, but may relate to the mother's own intrauterine and postnatal developmental trajectory (Price & Coe, 2000; Price, Hyde,

& Coe, 1999). In support, mother's age of menarche predicts adolescents' age of menarche (Styne & Grumbach, 2002), and this effect is not mediated by family conflict or father absence (Campbell & Udry, 1995). Nevertheless, there is some room for both biological and environmental explanations. Mother and daughter's age of menarche are consistently found to be moderately correlated (Graber & Brooks-Gunn, 1995), but the size of the correlation depends on environmental factors. For example, there is a mother-daughter correlation in the age of menarche in nondancers, but not in dancers, suggesting that dancer's exercise-rich environment overrode potential genetic links (Brooks-Gunn & Warren, 1988). Thus, a symphony of biological and social may advance pubertal timing when the environment is conducive to early and opportunistic reproduction. These factors appear developmentally early in a child's prenatal and postnatal development, or perhaps even earlier (in the mother's lifetime).

3.6] International Adoption Advances Puberty when Girls “Catch-up”

Although genetic transmission may account for early puberty in families characterized by stress and family discord, it is less likely an explanation for early pubertal maturation in internationally adopted or post-institutionalized children (Styne & Grumbach, 2002). Anecdotal observations in my own work with Russian and Romanian adoptees indicate early pubertal maturation. A series of studies by Proos and colleagues have found that Indian girls adopted into Sweden had earlier menarche (Proos, 1993; Proos, Hofvander, & Tuvemo, 1991; Tuvemo & Proos, 1993). A subset of these girls have very early onset of menarche and very short final height (Proos, Karlberg, Hofvander, & Tuvemo, 1993). Advanced menarcheal age was partially mediated by faster catch-up growth, infections, and later arrival age in Sweden (Proos, 1993; Proos et al., 1991; Tuvemo & Proos, 1993). It is interesting that accelerated catch-up growth after adoption likewise accelerated pubertal development since this resulted in a greatly reduced final height in the girls (Proos et al., 1993). Children lose one inch of linear growth for each 2 – 3 months of institutionalization in early development (Gunnar, Bruce, & Grotevant, 2000). Successful catch-up growth at first may appear to reverse the deleterious consequences of institutionalization, but subsequent early pubertal maturation may negate these initial benefits.

3.7] Other Factors, Mostly Endocrine or Biosocial, Advance Puberty

Other factors that may also advance pubertal timing include social rank and dominance. Monkeys who are higher ranked ovulate earlier than lower ranking females (Wallen & Zehr) and dominant female animals become pregnant earlier than subordinates (Cole et al., 2004). The mechanism for dominance and rank affecting puberty may be testosterone since some evidence indicates that testosterone advances puberty (Goy & Kemnitz, 1983). However, Zehr and colleagues did not find an effect of prenatal administration of testosterone on the pubertal timing but rather showed that prenatal handling advanced pubertal maturation, presumably through more socially or biosocially mediated mechanisms. Beginning with McClintock's demonstration of menstrual synchrony, there has been discussion of pheromonal regulation of pubertal timing (McClintock & Herdt, 1996). Pheromones are chemicals, frequently hormonal substances, which are released from the body

(e.g., sweat, urine, saliva) rather than into the bloodstream. Animal studies have long demonstrated that the presence of a biologically unrelated adult male can induce pulses of GnRH and ovulation in anestrus females (termed the “male effect”); and that the presence of a dominant female delays pubertal maturation in subordinate or, alternatively, an estrous female stimulates ovulation in conspecifics (termed the “female effect”) (Cole et al., 2004). These effects are demonstrated as pheromonally mediated in animals, through detection in the vomeronasal organ. It is difficult to generalize these findings to humans, however, since the vomeronasal organ in humans is vestigial, disappearing before birth. Nevertheless, evidence for pheromonally-mediated pubertal influences exists though the mechanism is unknown. Other studies indicate that contamination with environmental estrogens (i.e., in plastics or pesticides) may advance puberty in animals and humans (Ojeda & Terasawa, 2002).

3.8] Summary and Integration

Several environmental factors have been identified which can advance pubertal maturation, including race, nutrition, exercise and weight, low birthweight or postnatal growth, family context and conflict, familial or genetic transmission, adoption, dominance, and pheromonal signalling. Evidence linking nutrition and weight to pubertal timing invoke “critical weight” models in which girls must attain enough physical stature and body fat in order to sustain sexual reproduction. Seemingly contradictory evidence that low birthweight advances puberty instead invokes “fetal programming” hypotheses which argue that low birthweight girls are biologically prepared for low nutrition and weight gain, then experience advanced puberty when postnatal growth is accelerated. Thus, poor prenatal growth may have reorganized the setpoint for the weight necessary for an individual girl to advance through puberty. A similar model for early family conflict, harsh child rearing practices and insecure attachment emphasize the organizing role that early development holds for predicting later physical development and reproductive strategies. Genetic and intergenerational explanations cannot be ruled out from models for the effects of early socialization, but are likely complementary rather than mutually exclusive explanations. That international adoption advances puberty awaits a nongenetic explanatory mechanism. Taken together, these models emphasize that the match of the individual with their environment, both proximate (i.e., critical weight) and distal (i.e., fetal programming), provides a good indicator for how fast girls should mature physically and sexually. Girls may be placed on particular developmental trajectories early in development which may be changed or amplified during adolescence.

It should be noted that these studies often use age of menarche in girls as a marker for puberty, a relatively late pubertal indicator. This underscores that the onset of puberty is likely independent of proximate hormonal signals (though earlier organizational effects of hormones may be implicated) and environmental forces, some of which appear hormonally- or pheromonally-mediated, act by advancing the rate of pubertal maturation. The possibility remains, however, that distal forces (i.e., prenatal growth) have organized the setpoint for the maturation of the GnRH

pulse generator. It is unfortunate, however, that few studies have directly assessed rates of maturation in longitudinal studies (Brooks-Gunn & Warren, 1985).

4. Effects of reawakening the GnRH pulse generator

The downstream effects of GnRH pulses are primarily responsible for sexual maturation. Although the causes of the reawakening of the GnRH pulse generator has received the most empirical attention as the pubertal trigger, GnRH's main function is to control the synthesis and release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) from the anterior pituitary (Jennes & Conn, 2002). LH and FSH are released in intermittent pulses into the peripheral bloodstream (Dunkel, Alfthan, Stenman, Tapanainen, & Perheentupa, 1990), primarily at night. It is only during late adolescence and adulthood that pulses can be detected during the day (Styne & Grumbach, 2002). LH and FSH, in turn, act on receptors in the gonads to stimulate the release of estrogens, such as 17β -estradiol, and androgens, such as testosterone. In males, once the GnRH pulse generator is reawakened, there will be relatively consistent robust pulses of LH and, less so, FSH released from the anterior pituitary. In females, however, LH and FSH will be released more cyclically once negative and positive feedback loops of estrogen from the ovaries are established. A sudden surge in LH levels directly triggers ovulation in females, in part through estrogen interactions. Both sexes produce the 'male' and 'female' hormones, though concentrations vary greatly.

During sexual differentiation *in utero*, the fetal testes release testosterone and dihydrotestosterone which cause the masculinization of the brain and body, including the organizing development of the penis and scrotum. The male brain is also defeminized during fetal development, though estrogen is directly implicated. Testosterone, more easily than estrogen, crosses the blood-brain barrier, then testosterone is converted to estrogen in the brain by the enzyme aromatase (Hutchison, 1997). Meanwhile, Müllerian inhibiting hormone causes the degeneration of female sexual characteristics in the developing male. The default, however, is female so no signal is necessary from the ovary to stimulate the development of the female (Zahn-Waxler, Crick, Shirtcliff, & Wall, 2006).

4.1] Peripheral Hormones Develop Secondary Sex Characteristics

Primary sexual development refers to the maturation of the ovaries and testes, a sign of which is rising gonadal steroids. These gonadal steroids, in turn, cause the maturation of secondary sexual characteristics by acting on receptors throughout the body and brain.

Testosterone is considered an anabolic hormone because it facilitates growth and maturation. Testosterone exaggerates aggression, competition, dominance, and risk taking behavior in males (Mazur & Booth, 1998; Monaghan & Glickman, 1992; Sapolsky, 1997), particularly during pubertal transitions (Almeida, Anselmo-Franci, Rosa e Silva, & Carvalho, 1998), most likely because of the important evolutionary role of establishing social status and dominance during this life stage (Schaal, Tremblay, Soussignan, & Susman, 1996). Testosterone is primarily responsible for

genital growth in males, including the growth of the penis and scrotum; additionally, testosterone contributes to muscular enlargement. Once pubertal processes are underway, testosterone influences the GnRH pulse generator and the release of LH and FSH from the anterior pituitary through negative feedback (Hale et al., 1988; Sisk & Foster, 2004). Testosterone is present in juveniles, and has a reliable circadian rhythm, but it is not until Tanner stage 3 that the circadian rhythm appears adult-like (Butler et al., 1989). In pre-pubertal children, there is no gender difference in testosterone levels, but a large study of normally developing adolescents indicates that by Petersen Pubertal ratings of 3 (when signs of puberty are 'definitely underway'), salivary testosterone levels in adolescent boys and adult men are 3 to 3.5 times as high as girls and women (Granger, Shirtcliff, Booth, Kivlighan, & Schwartz, 2004). Importantly, adolescent boys with delayed pubertal development show rapidly advancing pubertal and sexual maturation when administered increasing concentrations of testosterone, demonstrating the significance of this steroid (Finkelstein et al., 1999; Finkelstein et al., 1998). Testosterone is also implicated in maintaining male-typical adipose tissue distribution (Ehrenreich et al., 1999).

Estrogen, primarily estradiol, include hormones released from the ovaries in females. Estrogen has receptors throughout the entire body and through diverse areas of the brain. Estrogen has neuroprotective benefits that encourage synaptic growth in the hippocampus (Woolley & Cohen, 2002), thereby facilitating learning and memory (McEwen, 1998). Estrogen levels in females are greater than males at certain phases of the menstrual cycle, although even in females, estrogen levels are nearly undetectable during menses and the early follicular phase and may be undetectable in a large percentage of pubertal-age females (Shirtcliff et al., 2000). A unique case report of a man born without the estrogen-receptor gene has also demonstrated the importance of estrogen in bone growth, skeletal maturation, osteoporosis, and epiphyseal maturation. Very high concentrations of estrogen in his system also suggest that negative feedback of estrogen is operational in men as well as women (Smith et al., 1994). In both sexes, estrogen levels rise during late puberty to encourage epiphyseal fusion (Frank, 2003; MacGillivray, Morishima, Conte, Grumbach, & Smith, 1998). The effect of estrogen on bone growth is biphasic with low levels of estrogen stimulating growth and high estrogen levels inhibiting growth in part by encouraging epiphyseal fusion and inhibitory interactions with insulin-like-growth-hormone (Fernandez-Garcia et al., 2002). Importantly, adolescent girls with delayed pubertal development show advancing pubertal maturation when administered increasing concentrations of estrogen in a double blind, placebo controlled trial (Finkelstein et al., 1999; Finkelstein et al., 1998). Estrogen causes breast development seen in girls. It also encourages fat deposits typical of the adult female body type in part by interacting with leptin. Adipose tissue also produces and stores estrogen levels, suggesting a reciprocal loop between estrogen, leptin and fat (Frisch, 1987). Cyclic changes in estrogen levels are also responsible for varying thicknesses of vaginal tissues in girls and the pubertal rise in estrogen accounts for the initial thickening of vaginal walls in pubertal girls; together with progesterone, estrogen also controls endometrial thickness (Fernandez-Garcia et al., 2002). A major difference between pubertal

maturation in boys and girls is that the endocrine control of pubertal development, once established, is tonic in boys but remains cyclical in girls (Ojeda & Terasawa, 2002). During the menstrual cycle, estrogen is largely responsible for stimulating the ovulatory surge by providing a positive feedback signal on the hypothalamus and anterior pituitary. Consistently elevated estrogen levels change LH receptor sensitivity to GnRH, resulting in the ovulatory surge of LH release. Ovulation is one of the last signals of pubertal maturation in girls (Terasawa & Fernandez, 2001).

Prior to the development of secondary sexual characteristics and even, perhaps the reawakening of the GnRH pulse generator, children mature through adrenarche, the maturation of the adrenal gland (Parker, 1991). Adrenarche is characterized by a steady rise in dehydroepiandrosterone (DHEA), DHEA-S, and androstenedione. The trigger for adrenarche is unknown, though it does not appear to be due to ACTH or the maturation of other components of the hypothalamic-pituitary-adrenal (HPA) axis, such as cortisol (Havelock, Auchus, & Rainey, 2004). Adrenarche begins two to three years earlier than gonadarche, with rising DHEA observed between six to eight years of age (Sumner et al., 1999), earlier in girls than boys. However, the rise in adrenal androgens is gradual, so concentrations of DHEA and androstenedione do not begin to exert effects on the developing body until some years after adrenarche and will continue to rise until around age 30 (Saenger & Dimartino-Nardi, 2001). The main developmental effect of adrenal androgens is the development of pubic hair, axillary hair, and body odor (Auchus & Rainey, 2004). DHEA is also a prohormone for testosterone, dihydrotestosterone and androstenedione, so about half of androgen exposure in girls comes from peripheral conversion from DHEA (Granger, Schwartz, Booth, Curran, & Zakaria, 1999). DHEA, like testosterone, also has anabolic properties and, like estrogen, it has neuroprotective and neurogenerative effects (Suzuki, Wright, Marwah, Lardy, & Svendsen, 2004). DHEA is a protective hormone that counteracts many negative effects of stress-related hormones like cortisol even though it is co-released with cortisol upon stimulation by ACTH. DHEA enhances learning, memory, and immunocompetence, protects neurons against the toxic effects of cortisol, and reduces anxiety and depression (see Majewska, 1995; see Wolf & Kirschbaum, 1999). Adrenal androgens are related to body mass and adiposity, although, unlike estrogen, the direction of the effect is unclear (Remer, 2000; Weise, Eisenhofer, & Merke, 2002). It appears that low birthweight and subsequent adiposity predispose children to an early adrenarche, especially girls (Charkaluk, Trivin, & Brauner, 2004). This relation to weight does not extend to height, as DHEA and androstenedione are not responsible for the mild growth spurt often seen in childhood (Remer & Manz, 2001). Interestingly, gonadarche and adrenarche are independent from each other, based on the observation that individuals with premature adrenarche undergo normal gonadarche and vice versa (Saenger & Dimartino-Nardi, 2001).

One of the hallmarks of adolescent development is the pubertal growth spurt, a time of life when individuals grow faster than at any other time of life, barring fetal and early infant growth. Rising levels of Growth Hormone, not surprisingly, is largely responsible for the growth spurt, although estrogen and, indirectly through estrogen, testosterone, are responsible for stimulating growth hormone release

(Ojeda & Terasawa, 2002). Growth hormone is an important permissive factor for pubertal maturation as growth hormone deficiency results in delayed puberty and growth hormone replacement therapy advances pubertal maturation (Andersen, Hariri, Pittelkow, & Rosenfeld, 1997). Growth hormone levels rise after the initial onset of puberty, with maximal levels around Breast Tanner stage 3 to 4 in girls or Genital Stage 4 in boys (Styne & Grumbach, 2002).

Another hormone implicated in the pubertal growth spurt is Insulin-Like Growth Factor I (IGF-I), discussed briefly above in its interaction with astroglial cells. IGF-I levels rise dramatically during pubertal development, with peak levels between stage I and II, or perhaps even earlier (Ojeda & Terasawa, 2002). Unlike growth hormone, rising IGF-I levels appear independent of gonadal steroids, in part because changing IGF-I is observed so early in puberty. Later in pubertal development, however, IGF-I and growth hormone interact a great deal to cause the pubertal growth spurt and final bone maturation (Styne & Grumbach, 2002). IGF-I is also implicated in advancing the age of first ovulation, another late pubertal event (Ojeda & Terasawa, 2002).

In sum, several peripheral neuroendocrine events are coordinated to varying degrees, thereby directly causing the development of secondary sexual characteristics which are more readily observed in the developing adolescent than hormonal events. These changes are often cyclical in girls, but tonic in boys. Once puberty is underway, steroid hormones like estrogen, testosterone and DHEA help regulate the neural system that originally triggered their maturation. This regulatory role of gonadal and adrenal steroids is usually inhibitory and helps keep the axis within a particular range of activation. However, it can also be excitatory as when persistently elevated estrogen triggers an LH surge and subsequent ovulation in girls. These hormones also interact in the periphery through cellular interactions or through conversion from one hormone to another by enzymes like aromatase. Interestingly, these enzymes are also located in the brain, suggestive of complicated steroidal regulation occurring at a neural level. It is primarily at the gonadal level that sex differences in hormonal activation occur, although the anterior pituitary also shows consistent sex differences.

4.2] Secondary Sexual Characteristics are Visible Signs of Puberty

This review has consistently referred to secondary sexual characteristics and to stages of pubertal development, assuming the reader has some familiarity with these events. A brief description of pubertal events, nonetheless, is warranted. Over four decades ago, Tanner's (1962) book described five stages of pubertal development of breast and pubic hair for girls, and genital and pubic hair for boys. These stages, with accompanying photographs, have become the standard range of stages of pubertal progression, with one notable exception being the Petersen Pubertal Development Scale (Petersen, Crockett, Richards, & Boxer, 1988).

4.2. a) Girls

Breast development is the first sign of puberty in 83% of girls (Marshall & Tanner, 1969). For breast development, stage 1 is the juvenile state with no palpable breast tissue and areola that are not pigmented. For white girls, the

average age of breast stage 2 is near 10 and a half or 11 years of age, with an age range from 7 to 13 years of age (Styne & Grumbach, 2002). Stage 2 corresponds to the first sign of breast development in girls, when the areola has gotten bigger and the breasts have begun to grow to about the size of a pea, but will not extend outside of the areola. Girls take approximately 10 to 11 months to advance from stage 2 to stage 3 (Marshall & Tanner, 1969). Stage 3 shows more breast tissue that extends beyond the areola “like a donut” and enlarged nipples are becoming pigmented. Breast development contains information to other males and females about social information. Such social signaling probably begins around stage 3 of development when the breast tissue extends beyond the areola (Brooks-Gunn & Warren, 1985). Girls take about 10 to 11 months to advance from stage 3 to stage 4. At stage 4, breast development and areola pigmentation continue, and the breast and areola are distinct tissues, with the areola and nipple forming a second mound on the breast. Girls take, on average, almost two years to advance from stage 4 to stage 5, although individual differences are very broad. Girls who advance quickly through stage 2 can be expected to also advance quickly through stage 3, although advancement to stage 4 is uncorrelated with earlier velocities. Some girls advance through stage 4 so quickly that it cannot be detected (Marshall & Tanner, 1969). At stage 5, the areola and nipple no longer project from the breast, regardless of the eventual size of the breasts. Girls are between 11 and a half and 18 and a half when reaching stage 5. It takes girls on average 4 years to advance from stage 2 through stage 5, though the interval may range from one and a half years to over six years (Marshall & Tanner, 1969), underscoring the importance of the duration of puberty as a measure of interest when considering the timing of puberty. Duration of puberty is not predicted by the age of onset (Marshall & Tanner, 1969).

Pubic hair growth is the first sign of puberty in approximately 16% of girls, with less than 5% of girls advancing to pubic stage 2 or 3 without measurable breast development. Stage 1 shows no pubic hair development. Stage 2 is difficult to examine because the hair is fine and light colored. For white girls, the average age of pubic stage 2 between eleven and 11.5 years of age (Marshall & Tanner, 1969). Girls take about seven months to advance to stage 3. Stage three shows dark and coarse hair sparsely extending over the pubis. Stage 3 pubic hair is seen most commonly with stage 3 or 4 breast development. Girls take about six months to advance to stage 4 from stage 3. At stage 4, the amount of coarse and curly hair increases, but the hair does not extend to the upper corners or down to the thighs. It will take girls approximately 15 months to advance to pubic stage 5, with most girls taking two and a half years to progress from stage 2 to stage 5. Girls are almost 14 and a half plus or minus one year when attaining pubic stage 5. At stage 5, the pubic hair has the full triangular pattern like an adult woman with hair also extending to the upper thigh. Girls frequently are not at the same stage of breast and pubic hair development at a given time. Less than half of girls will be concordant across these events, likely because they are under different endocrine controls. Being more than one stage discordant is less common, but certainly not rare (Marshall & Tanner, 1969). Girls usually show breast development before pubic hair development, but because they advance more quickly through pubic stages, 61% will demonstrate stage 5 pubic development before stage 5 breast

development (Marshall & Tanner, 1969). It is interesting that researchers frequently expect girls' breast and pubic development to be at the same stage of development, since it takes 4 years to progress from breast stage 2 to 5 and only two and a half years to progress from pubic hair stage 2 through 5.

The growth spurt, or peak height velocity, occurs early in girls at around age 12. It occurs about a year after the first sign of breast development when 51% of girls are breast stage 3 and 64% are pubic hair stage 2 or 3 (Marshall & Tanner, 1969). However, the observation that the peak growth occurs in early to mid-puberty suggest that girls have had accelerated growth rates for some time, perhaps even before the first sign of breast development (Brooks-Gunn & Warren, 1985). Peak height velocity occurs before menarche in nearly all girls (Marshall & Tanner, 1969). Girls may continue to grow a little after reaching peak height velocity, though only an inch or two is anticipated after they first menstruate.

Menarche, when girls have their first menstrual period, is probably the only pubertal event which is clearly observable and dichotomous. Nevertheless, its onset is not always accurately recalled by girls or their mothers and it is a poor measure of pubertal onset because it is a relatively late occurring event (Brooks-Gunn & Warren, 1985). Sixty-two percent of girls are at breast stage 4 and 63% are at pubic stage 4 when they first menstruate, respectively. The average age of menarche is between 12 and a half and 13 and a half, almost two years after girls first experience breast development on average (Marshall & Tanner, 1969).

First ovulation can occur with the first menstruation, or in at least one case, can lead to pregnancy before the girl has an opportunity to menstruate (Susman, Schmeelk, Ponirakis, & Garipey, 2001). More commonly a few menstrual periods are experienced before ovulation and it may take up to two years before menstrual periods are regular (Terasawa & Fernandez, 2001).

4.2. b) Boys

Research on puberty in boys does not have the richness of information that research on puberty in girls contains, although there are specific events which have been described (Tanner, 1962).

The first pubertal event in 98 to 99% of boys involves the development of the genitals. The use of an orchidometer made of wood (Prader, 1966) or chocolate (Bhalla & Williams, 2001) renders the measurement of boys' testicular size fairly precise. At genital stage 2, the testes have begun to grow and appear rougher and redder. The testicular size is between 2.5 and 3 centimeters (Genentech, 1997). There are no changes in the penis yet. Boys reach genital stage 2 at 11 years and 8 months on average although the age of reaching genital stage 2 varies from 9 to 13 and a half years old (Styne & Grumbach, 2002), with a substantial subset attaining puberty even later up to age 15 (Marshall & Tanner, 1970). Boys will advance to genital stage 3 on average in 13 months, with a range from five months to just over two years. At genital stage 3, the testicular size is between 3 and 3.5 centimeters and the penis has started to grow in length but not width. Boys will take on average nine and a half months to advance from genital stage 3 to stage 4 (Marshall & Tanner, 1970). At stage 4, the testicular size is between 3.5 and 4 centimeters and

the penis has started to grow in terms of both width and length. Boys will advance to genital stage 5 on average in one year, with a range of four and a half months to almost two years. Most boys will advance from stage 2 to 5 in about three years, with genital maturation rates ranging from one year and seven months to over four years and 8 months (Marshall & Tanner, 1970). At stage 5, the testicular length is greater than 4 centimeters and the penis is adult-like in terms of width and length. Self-reported pubertal development of advanced genital stage in boys may be challenging since the distinction between stage 4 and 5 is subtle and assumes that the penis has stopped growing for some time before boys would likely recognize it as 'adult-like' (Klimes-Dougan, Hastings, Granger, Usher, & Zahn-Waxler, 2001). It is interesting that some boys advance from genital stage 2 to stage 5 in the same amount of time that other boys will advance from genital stage 2 to stage 3.

Some time after boys' show advancing genital staging, their pubic hair begins to grow in much the same way as girls. Although some girls show breast development first and others show pubic hair development first, boys almost exclusively show substantial genital development first. Boys are almost 13 and a half before pubic hair begins to develop, although this estimate is likely overestimated. At pubic stage 2, 13% are concurrently in genital stage 2, 45% are in genital stage 3 and 41% are in genital stage 4 (Marshall & Tanner, 1970). Pubic stage 2 shows sparse growth of light hair that is usually straight near the base of the penis. Boys take about five months, with a range of one to ten months to advance to pubic stage 3. At stage 3, pubic hair is darker and coarser, but is just at near the base of the penis. At pubic stage 3, 79% of boys show advanced genital development of stage 4 or 5. Boys advance from pubic stage 3 to stage 4 in about five months, with a narrow range of about four to six months (Marshall & Tanner, 1970). At stage 4, pubic hair is adult-like in type and texture, but it does not yet have the full triangular pattern and does not extend toward the thighs. Boys advance from pubic stage 4 to stage 5 in about eight months, with a range from two months to almost a year and a half (Marshall & Tanner, 1970). At stage 5, the hair shows the full inverse triangle and spreads to the thighs. It takes boys just over a year and a half on average to advance through the stages of pubic hair development with a range from about 10 months to over two and a half years. It is also interesting that boys proceed through the genital stages in three years on average and through the pubic hair stages in a year and a half. As with girls, it is surprising that researchers expect genital and pubic Tanner staging to be parallel since they rarely are within the individual. Most boys show greater genital stages than pubertal stages which does not equalize (since pubic hair shows a faster maturation rate) until pubic hair stage 4 or 5.

Another noticeable component of pubertal development in boys is the attainment of peak height velocity or their growth spurt. Boys are usually nearly 14 years old when they show peak height velocity which means that boys have several more years to grow than girls before experiencing a growth spurt (Brooks-Gunn & Warren, 1985). While girls show their growth spurt early in development, most frequently in breast stage 3 and pubic hair stage 2 or 3, boys show their growth spurt much later. Approximately 74% of boys show their growth spurt in genital stage 4 (Marshall & Tanner, 1970). The neuroendocrine control of the bone growth

and epiphyseal fusion is estrogen, which girls have more abundantly than boys (MacGillivray et al., 1998). Boys experience less strict neuroendocrine control over long bone formation and the attainment of adult stature, so it is not uncommon for boys to continue growing well into their 20s, especially if they don't show their growth spurt until age 16 or 17 (Styne & Grumbach, 2002). The relationship between pubic hair development and the growth spurt is variable, such that the growth spurt coincided with pubic stage 2 in 32% of boys, stage 3 in 26% of boys, and stage 4 in 34% of boys (Marshall & Tanner, 1970).

Spermarche refers to the first ejaculation, which occurs at night as the first nocturnal emission in 26 to 53% of boys and through masturbation in 13 to 58% of boys (Adegoke, 1993; Downs & Fuller, 1991). Like menarche, spermarche is a dichotomous event although a single measurement of sperm production in adolescent males may not discover spermarche, and approximately one week's assessment may be necessary to capture sperm production (Kulin, Frontera, Demers, Bartholomew, & Lloyd, 1989). There is some evidence that recollection of first ejaculation is relatively reliable (Downs & Fuller, 1991). The average age of spermarche has been estimated to be around age 14 (Adegoke, 1993; Gaddis & Brooks-Gunn, 1985; Kulin et al., 1989), although others suggest it is earlier, around age 12 or 13 (Downs & Fuller, 1991; Fava et al., 1989; Qin, Mortensen, Agerbo, Westergard-Nielsen, & Eriksson, 2000). The latter is consistent with the idea that spermarche is a rather early pubertal event, occurring around pubic hair stage 2 or 3 (Qin et al., 2000), genital stage 2 to 4, and prior to the growth spurt (Qin et al., 2000). Examining spermarche may be difficult because few boys (23%) tell anyone it has occurred (Downs & Fuller, 1991).

Other markers of puberty, such as when the voice deepens or facial hair grows, convey social information to others. These markers have not been specifically pursued as an index of puberty although they are included in the Petersen Pubertal scale (1988). Other studies considered the male-typical and female-typical body fat and muscular distribution as a pubertal index (e.g., Ehrenreich et al., 1999), but individual differences in body weight (i.e., obesity, exercise regime) may overwhelm this measure of pubertal development. There are few visible signs of adrenarche in boys and girls, other than the development of pubic hair occurring years after the initial rise in adrenal androgens.

4.3] Summary and Integration

Secondary sex characteristics refer to the physical development of the body as pubertal maturation occurs. Most pubertal processes, including adrenarche, occur earlier in girls than boys.

First, breast development is triggered by estrogen when girls are about 11 years old, and it will take 4 years on average before breast development will be complete. Pubic hair develops when girls are about 11 and a half upon a gradual increase in adrenal androgens after adrenarche. It will take girls about two and a half years to advance through the pubic hair stages. Sex steroids cycle for some time before high estrogen stimulates endometrial thickening and subsequent drops in estrogen and progesterone trigger first menstruation. Menarche occurs almost

two and a half years after the first sign of pubertal development, when girls are about 13 and a half years old. A positive feedback loop with estrogen stimulates a sudden surge in LH and first ovulation ensues. This is the last pubertal event to occur in females. Wide variations in the timing and duration of each developmental stage, and the observation that breast and pubic hair develop at different times, rates, and through different endocrine control suggest that many girls will not have concordant Tanner stages for breasts and pubic hair.

In boys, the genitals start to develop around 11 years and 8 months of age and will be adult-like three years later, on average. Testosterone is primarily responsible for genital development. Boys almost exclusively show genital development before pubic hair. Pubic hair begins to develop by age 13 and a half and will be adult-like by about a year and a half later. Adrenal androgens and peripheral conversion of testosterone are primarily responsible for pubic hair development in boys. Testosterone, LH and FSH together contribute to spermatogenesis, the first ejaculation in boys. This event is an early pubertal event, occurring when boys are about 13 years old. Although the growth spurt occurs early in girls, boys typically do not attain peak height velocity until genital stage 4. Growth hormones and estrogen are implicated in the growth spurt in boys, with long bone fusion not occurring unless estrogen is present. Boys can typically continue growing into their college years. Other events, such as when the voice changes or when boys get facial hair, have received little empirical attention.

Some consistent themes emerge from this review: (a) different hormones contribute to the maturation of different pubertal processes; (b) these events are triggered at different times and maturation rates vary considerably from months to years; (c) the age of onset of puberty varies greatly from one individual to another; (d) the maturation rate of puberty also varies greatly from one individual to another; (e) boys and girls begin maturing at different times and rates although some of the underlying neuroendocrinology (as with estrogen and bones or adrenal androgens and pubic hair) may be similar; (f) even with similar neuroendocrinology, events which are early in girls may be late pubertal events with boys, as with the growth spurt. Although considerable evidence has indicated that the timing of puberty in relation to one's peers is significant, much less attention has been paid to the rate of maturation after pubertal onset, though this may be a few months in one child and as much as 6 or 7 years in another. The rate of maturation is not predicted by the age of onset of puberty, so these may contain distinct developmental information. Longitudinal studies are necessary to address maturation rates, especially since retrospection may not be adequate even for discrete events. Even less effort has addressed the concordance between one pubertal event and another, so it is difficult to know if adolescents who are off-time in one aspect of development differ from those mature synchronously. One study provides an excellent example of possible implications of pubertal synchrony. Girls who show advanced breast development before their growth spurt are more feminine and sexually precocious whereas girls who show the growth spurt first rate career attainment as more important than marriage and children (Brooks-Gunn & Warren, 1988). A guideline proposed by Brooks-Gunn and Warren (1985) include five maturational parameters of pubertal change: status, timing, rate, synchrony and differential salience of maturational

event. Arguably, only the first two have received much empirical attention, highlighting the wealth of future insights that can be gained by considering the suite of biosocial changes that occur in pubertal individuals.

5. Select Brain Maturation Linked with Pubertal Development

The first section of this review focused on top-down pubertal events where central changes in the hypothalamus influence peripheral hormone release and subsequent sexual maturation. This section will focus instead on bottom-up effects of puberty and steroid hormones on brain development. Many of these feedback effects will not be evident until the GnRH pulse generator is activated. Age- and puberty-related changes in brain maturation have begun to be explored in structural, functional and PET studies in children and adolescence. The purpose of a protracted development for brain maturation may maximize neural plasticity and allow the individual to develop in line with the particular constraints of their early and concurrent environment (Andersen, 2003). Much of this work focuses on age-related changes in adolescents, but this review will highlight when they investigate or implicate pubertal or hormonal changes. Brain maturation in adolescents is both steroid-dependent and –independent. This distinction is useful but imprecise, as steroid-dependent and –independent brain areas frequently interact (Nelson, Leibenluft, McClure, & Pine, 2005). A general theme will categorize steroid-dependent areas as related to reproduction (Sisk & Foster, 2004), including areas implicated in reward, risk, social and appetitive cues (Dahl, 2004; Keverne, 2004), which are distantly related to reproduction (Insel, 2003).

5.1] Structural Brain Changes in Areas Responsive to Hormones

Structural brain changes in adolescence is marked by competitive elimination, myelination, dendritic and axonal arborization (Giedd, 1997). Global changes in children between the ages of 7 and 16 include age-related increases in cortical volume, reductions in grey matter and concordant increases in white matter (Sowell, Trauner, Gamst, & Jernigan, 2002). An increase in cerebral spinal fluid volume in the ventricles provides additional evidence for competitive elimination in the brain (Sowell et al., 2002). An ongoing MRI investigation of highly screened normally developing children by Giedd and colleagues support these global brain changes in addition to more subtle maturation. Lateral ventricle volume increased with age, with most maturation occurring after age eleven (Giedd, 1997). Amygdala volume increased throughout adolescence in males, but was a trend in females; conversely, hippocampal volume increased across adolescence in females, but not males (Giedd, 1997). These result are consistent with steroid-dependent maturational changes, as the amygdala is rich with testosterone receptors and the hippocampus is one of the main sites for estrogen-dependent synapse formation (Giedd, Vaituzis et al., 1996). Further, there was evidence for regional nonlinear changes in grey matter volume during adolescence, consistent with the notion of a prepubertal increase and a postpubertal loss in grey matter (Gogtay et al., 2004). In males, but not females, the caudate and putamen volume decrease with age throughout childhood and adolescence (Giedd, Snell et al., 1996). In both sexes, the

midsagittal corpus collosum linearly increase in size from age 4 to 18 (Giedd, Rumsey et al., 1996), with a parallel finding from a longitudinal investigation indicating the greatest increases in corpus collosum evident in childhood (Giedd et al., 1999).

Some of Giedd's assertion that these brain changes are related to pubertal hormones is based on evidence that many of these structures are dense with steroid hormone receptors (Cameron, 2004a, , 2004b; Giedd, Vaituzis et al., 1996). Two main types of estrogen receptors include alpha ($ER\alpha$) and beta ($ER\beta$) (McEwen, 2002; McEwen, 2001). In rats, estrogen receptors are located abundantly in the hippocampus, hypothalamus, and all throughout the limbic system. In humans, $ER\alpha$ mRNA is expressed throughout subnuclei in the amygdala, with the highest levels of $ER\alpha$ found in the amygdala-hippocampal area (McEwen, 2002; McEwen, 2001). Some signaling is also found in the bed nucleus of the stria terminalis, although testosterone receptors dominate there (Monaghan & Glickman, 1992). $ER\alpha$ receptors are also found in areas of the hypothalamus beyond those structures involved in the GnRH pulse generator such as the supraoptic and preoptic areas. $ER\beta$ mRNA is profusely found throughout the hippocampus. Both $ER\beta$ and $ER\alpha$ mRNA can be seen through the cerebral cortex including the entorhinal cortex, one of the pathways to the hippocampus. The basal ganglia and thalamus have low $ER\alpha$ and $ER\beta$ mRNA expression (Ostlund, Keller, & Yurd, 2003). Androgen receptors largely overlap with estrogen receptor distribution in rats and monkeys.

Other evidence that these structural brain changes are related to pubertal hormones comes from a structural MRI study in humans by De Bellis and colleagues (De Bellis, 2001). The age-related reductions in grey matter and increases in white matter and the corpus collosum in children aged 7 to 17 years old were redundant with puberty-related changes measured by Tanner staging. There was also an interaction with gender such that these developmental changes were relatively faster in boys than girls. The authors concluded that testosterone expression in the brain accounts for increased myelination while estrogen contributes to early dendritic pruning (De Bellis, 2001). It is notable that Giedd likewise examines puberty-related changes in brain structures and finds that age- and puberty-related maturation of limbic structures are similar. In sum, after the onset of puberty, there are structural changes in the limbic system in areas dense with sex steroid receptors.

5.2] Animal and PET Studies Demonstrate Alterations Across Diverse Neurotransmitter Systems

Although PET studies are often limited to certain populations (e.g., epileptics), they provide insight into the neurotransmitter systems that mature during adolescence. Chugani and colleagues (1987) found that local cerebral metabolic rates for glucose, indicating which brain areas are the most energetically active, shows high metabolic rates throughout childhood in grey matter which is maintained until approximately 9 years of age. At this early adolescent stage, metabolic rates in grey matter begin to decline, reaching adult levels the late teenage years. The authors interpreted this profile to indicate initial overproduction and subsequent elimination of neurons, synapses and dendritic spines in the

developing brain. Another study indicated cerebral maturation persisted until adolescents were 16 to 18 years old (Chugani, 1998). Finally, a study using a ligand for GABA indicated that subcortical regions reached adult values of metabolic rates by the age of 14 to 17 years while cortical regions reached adult levels in the early 20s (Chugani et al., 2001). Although clearly there is more to be learned from PET studies and ligand-specific metabolic rates, these few studies begin to demonstrate adolescent maturation in subcortical and cortical activity. Combined with animal studies, they hint toward the involvement of sex steroids in the maturing brain. Animal studies have shown that sex steroids interact with most neurotransmitter systems, including serotonin, acetylcholine, noradrenaline, dopamine, endogenous opioids, oxytocin and vasopressin (Cameron, 2004a; Carter, 1998; Taylor et al., 2000). Broad changes in the adolescent cerebral cortex may be further shaped and sculpted by environmental inputs provided by sex steroids directly and indirectly by interacting with neurotransmitters. Adolescence may be a sensitive period for further steroid-dependent organization of neural circuits mediating reproductively relevant social behaviors (Sisk & Foster, 2004).

5.3] Functional MRIs Show Heightened Activity to Affective Stimuli

Functional MRI studies have contributed to the third progressive step made toward understanding the adolescent brain. An overarching model proposed by Nelson and colleagues (Nelson et al., 2005), based largely on fMRI investigations of social behavior, emphasizes the synchrony between steroid-dependent and – independent maturational changes in the brain. They propose that three neuronal circuits dedicated to the processing of social information mature at different times across childhood. The first circuitry, the detection node, is dedicated to categorizing social information and includes such areas as the inferior occipital cortex, the temporal cortex and the fusiform face gyrus. The detection node is fully mature before adolescence. The second circuitry, the affective node, matures during adolescence and involves areas related to reward and punishment. Areas such as the amygdala, hypothalamus, ventral striatum, septum and bed nucleus of the stria terminalis, frequently mentioned above, are highly regulated by gonadal steroids, particularly when social information is novel. The affective node, then, is thought to mature with the pubertal trajectory. The third node is cognitive and regulatory. It involves structures related to theory of mind operations, such as the dorsomedial prefrontal cortex, as well as structures related to inhibitory responses and goal directed behavior, such as the dorsal and ventral prefrontal cortex. The cognitive-inhibitory node demonstrates slow development across most of childhood and does not reach full maturation until early adulthood. Its developmental trajectory is influenced by age and experience more than hormones, though hormones may demonstrate a secondary effect. That is, structures in the affective and cognitive-inhibitory nodes extensively interact such that the cognitive-inhibitory node will eventually regulate the affective node. In adolescents, however, the cognitive-inhibitory node may not be mature enough yet to dominate the affective node such that adolescents may be overwhelmed by socially relevant reward cues (Dahl, 2004).

fMRI studies in adolescents have generally explored tasks that target the affective node in order to understand how adolescents process reward and

punishment cues. Ernst and colleagues (Ernst et al., 2005) developed a wheel of fortune task to understand adolescents' propensity for risk taking and reward seeking behavior. Their results revealed greater responses of the nucleus accumbens and amygdala when winning than when losing, but adolescents in particular activated the nucleus accumbens while adults activated the amygdala, suggestive of heightened sensitivity to reward more than punishment (van Honk, Schutter, Hermans, & Putman, 2003). Other fMRI studies have examined the brain processing emotion-laden faces. Adolescents who reported more fear while viewing fearful faces showed right amygdala activation during the threat condition and left amygdala activation in the safe condition (McClure et al., 2004). Compared to adults, adolescents showed greater activation in the anterior cingulate, orbitofrontal cortex and right amygdala in response to fearful faces (McClure et al., 2004), and demonstrated more activity in the right temporal lobe when viewing subsequently remembered fearful faces (Nelson et al., 2003). The activation patterns appear specific to particular emotion-responses, a finding in keeping with the evolutionary significance of the limbic system (LeDoux, 1996). Adolescents had heightened activity in the anterior cingulate when viewing subsequently remembered angry faces, but less activity than adults in the anterior cingulate when viewing happy faces (Nelson et al., 2003). Adults, but not adolescents, showed heightened activity in the hippocampus when viewing subsequently remembered neutral faces (Nelson et al., 2003). These findings extend to when affective stimuli is masked as well (Pine et al., 2001). These studies suggest that adults activate areas related to attentional demands when viewing emotion-laden faces while adolescents spend more energy attending to the emotional content of the faces and consequently activate areas related to affective processing (McClure et al., 2004). It is interesting that these normative findings of altered amygdala activation in response to fearful faces in adolescents appear exaggerated in depressed adolescents (Pine et al., 2004).

In addition to developmental changes in the affective node, there may also be gender differences. In response to emotion-laden faces, female adolescents (compared to children) show progressive increases in prefrontal activation relative to amygdala activation while males do not show age-linked changes in amygdala or prefrontal activation in response to fearful faces (Killgore & Yurgelun-Todd, 2001). Similarly, adult women activated the orbitofrontal cortex and amygdala when viewing threatening cues while adult men and adolescent boys and girls did not (McClure et al., 2004). These studies suggest there is an interaction between sex and development in the maturation of the affective node.

5.4] Summary and Integration

The brain matures throughout childhood and adolescence. These changes are more or less synchronized in one individual than another. Areas that mature along the pubertal trajectory are rich with sex steroid receptors, with notably overlapping testosterone and estrogen receptor gene expression, across a wide range of neurotransmitter systems. These areas are frequently in the limbic system, encompassed in Nelson's model (Nelson et al., 2005) for the affective node. Brain areas consistently related to affect, mood, risk, and reward frequently mature during adolescence. fMRI studies indicate heightened activation of affect related

brain areas in adolescents but attention related brain areas in adults viewing emotion faces. Although the structure of a particular brain area does not necessarily implicate a particular behavior (Davidson, 2003), nevertheless, behavioral dysregulation in adolescence clearly implicates developmental changes in affect, mood, risk, and reward. This conceptual model has been detailed elsewhere (Dahl, 2004).

6. Normative Behavioral Alterations During Pubertal Transition

The next section will briefly review behavioral changes frequently observed in adolescents, emphasizing the possible neuroendocrine underpinnings of these behavioral changes (Spear, 2000). A comment on the distinction between *normative* and *clinical* behavior problems is worthwhile. A developmental psychopathology perspective emphasizes that normative developmental trajectories can inform research on psychopathology, and that the etiology of psychopathology can likewise point to mechanisms for biological vulnerabilities (Cicchetti & Cohen, 1995). A false dichotomy between normal and clinical is created below with some attempts made subsequently to integrate across the full range of behavior. For example, aggression, parent-child conflict, and risky behavior are all hallmark symptoms of delinquency, oppositional defiant and conduct disorder. Moodiness, negative affect, irritability and sleep disturbances are central features of depression. Body image issues can become pathological as eating disorders. Eighty percent of adolescents will navigate this life stage without clinical range problem behavior (Steinberg & Morris, 2001). Exploring hormonal changes at puberty can make important strides towards understanding the challenges that all adolescents face and may point toward reasons for some adolescents to develop behavior problems.

6.1] Eating Behavior Increases in Adolescents

There is some evidence that the pubertal growth spurt, combined with rising growth hormone and IGF-I levels, is associated with a notably enhanced rate of eating behaviors in humans, primates and rats (Spear, 2000). Adolescents also show elevated metabolic activity and developmental hyperphagia, suggesting that they spend more time and energy searching for food and find the attainment of food more rewarding. Dopamine levels increase in the reward circuitry of the brain when adolescents obtain food. A provocative extension of this idea implicates the consummatory drive toward drug experimentation when a tendency to take metabolic reinforcers extends to drug reinforcers (Spear, 2000).

Most steroid hormones are directly related to metabolism and energy, so it is not surprising that puberty marks changes in eating behavior. Changes in leptin and the accumulation of body fat at the onset of puberty have been frequently linked (Cacioppo et al., 2002). In girls, leptin rises as body fat increases (Matejek et al., 1999). Changes in leptin interact synergistically with estrogen at the onset of puberty, across the menstrual cycle, and throughout the entire female life cycle (Plant, 2002). Increased body fat allows metabolically active estrogen to exert effects throughout the body. In boys, leptin levels increase near the early stages of puberty, then declines while pubertal development is still underway (Cacioppo et al.,

2002). This may be because testosterone suppresses leptin synthesis. The sharp pubertal rise in testosterone encourages a decrease in body mass by suppressing leptin and an increase in muscle mass related to direct anabolic effects of rising testosterone in late puberty in males (Kiess et al., 1995).

6.2] Adolescents Need to Sleep More, But They Get Less Sleep

The sleep habits of adolescents has been diligently delineated by Carskadon and colleagues (Carskadon, Acebo, & Jenni, 2004). Adolescents show decreasing total sleep time, a tendency to delay the timing of sleep, and an increased level of daytime sleepiness (Carskadon, 1990). Combined with early school attendance, this results in adolescents requiring over two additional hours of sleep a night than they actually get by grade 12 (Carskadon et al., 2004). The adolescent preference for staying up late is not entirely culturally based, as laboratory and animal studies show similar phase delays toward going to bed and waking up later in the day (Spear, 2000). Further, this phase delay is tied directly to pubertal maturation, with Tanner stage 5 adolescents showing 40% less slow wave sleep than Tanner stage 1 individuals even when holding the actual amount of sleep constant in a laboratory setting (Carskadon et al., 2004).

Hormones are implicated frequently in the regulation of sleep. More mature children show a later offset time for melatonin secretion, even when on a controlled sleep schedule (Carskadon, Acebo, Richardson, Tate, & Seifer, 1997). Carskadon suggests that sleep is governed by circadian variations in melatonin secretion and activity in the suprachiasmatic nuclei of the hypothalamus as well as the gradual accumulation and dissipation of slow wave sleep occurring each day. Both of these processes are dysregulated in adolescents, in part because their synchrony is disrupted. That is, adolescents show a high propensity for slow wave activity in the middle of the day, favoring a 'siesta' (Carskadon et al., 2004).

Relations with gonadal steroids appear initially paradoxical: Androgens and estrogens are positively related to activity levels, yet puberty marks rising levels of fatigue and more variable swings from alertness to drowsiness. Further, early maturing girls report being overtired more frequently than their on-time counterparts (Buchanan et al., 1992). This paradox may be resolved by an *adjustment model*: pubertal changes in steroid hormone concentrations cause biological disequilibrium to which children must adjust. This leads to more frequent and more variable energy levels. After adjusting to the new biological state, high levels of steroids, notably DHEA and androstenedione, exert a positive influence on energy and activity levels (Buchanan et al., 1992). Thus, sleep, energy and activity represent a model system for understanding how variability and synchrony can contribute greatly to our understanding of the neuroendocrinology of puberty, while absolute hormone levels add paradoxes and confusion.

6.3] Hormones Poor Explanation For Moodiness and Negative Affect

Although popular ideas like *Raging Hormones* suggest that moodiness is the hallmark of pubertal maturation, in fact, it is more likely that adolescents are more moody than adults, but no more moody than children (Steinberg & Morris, 2001). Adolescents experiencing early puberty, however, are at heightened risk for

psychological distress and negative affect. Girls with precocious puberty are at heightened risk for social and emotional problems which often abate when they get treatment (Xhrouet-Heinrichs et al., 1997). Ge and colleagues (1996) compared early maturing girls to on-time and late-maturing girls. Early maturers experienced highest levels of psychological distress from eighth through tenth grades, noticeably later than their initial menarcheal age. Negative affect in early maturing girls was predicted by several longitudinal measures, including early psychological symptoms, father's hostile feelings and behaviors, and involvement with deviant peers, including older males. These factors did not predict psychological distress in on-time or late maturing girls, suggesting that pubertal timing moderated the association between early life stress and moodiness. This path model fits with the idea that early maturation combined with life stressors can disrupt girls' developmental trajectory and serve as pathways toward depression and anxiety problems (Hayward & Sanborn, 2002). This study was based on normal range of psychological distress in a study of normal adolescents, so it is unlikely that many girls were within the clinical range of problem behavior.

The relationship between hormones and moodiness or negative affect is rife with paradoxes. Gonadal steroids protect individuals from rapid mood swings by directly modulating central nervous system activity and keeping neural activity in affective circuitry within acceptable range (Rubinow, Schmidt, Roca, & Daly, 2002). Testosterone, estrogen, and DHEA have mood enhancing properties. Likewise, estrogen has mood enhancing properties and estrogen combined with antidepressants elevates mood and lifts depression exponentially better than antidepressants alone (McEwen, 2002). At least one study in adolescents revealed that boys with high estrogen and a high testosterone/estrogen ratio had less sad affect and emotional tone (Susman, 1985). One case study showed testosterone administration in an individual with much delayed puberty resulted in enhanced mood and well-being (Ehrenreich et al., 1999). Experimental studies of DHEA treatment in elderly humans have revealed that DHEA enhances mood and has antidepressant effects (Wolf & Kirschbaum, 1999). How can these steroids enhance mood if adolescents are supposed to be at risk for mood swings?

One possibility is that these studies did not target adolescents, so these hormones behave fundamentally different at this developmental stage than they do in adults. In support, a powerful placebo controlled, cross over design in adolescents with delayed pubertal onset revealed few effects of testosterone administration (for boys) or estrogen administration (for girls) on mood (Susman et al., 1998). This study's measure of 'mood' was the child-behavior-checklist which was designed to assess clinical and subclinical level behavior problems more than normal mood variability. Another study found that testosterone predicted moodiness, though the age range included presumably included mostly prepubertal individuals (Essex et al., 2002). This possibility awaits further exploration before it can be rejected or accepted.

Another possibility is that the relationship between hormones and mood is curvilinear, with low and high hormones being related to negative affect. Warren and Brooks-Gunn (1989) revealed a curvilinear relationship in which rising estrogen

levels predicted depressive affect when estrogen levels were low, but declining estrogen predicted depressive affect when estrogen levels were high. Weiner and colleagues (1989) found that negative affect was highest in polycystic ovary syndrome women with slightly elevated testosterone levels, while negative affect was lowest in women with low to normal testosterone levels or extremely high testosterone levels; it should be noted that polycystic ovary syndrome is characterized by elevated testosterone levels, so extremely high testosterone places these women in the male-typical range. A provocative extension of this idea is that the curvilinear relationship between testosterone and mood may be caused by different factors. Adult men with low testosterone may have depressed affect because they do not benefit from the mood enhancing benefits of the hormone; men with high testosterone may have depressed affect because their high testosterone levels have made them more likely to be unemployed, have poor marriages, and engage in risk behavior (Booth, Johnson, & Granger, 1999). This type of relationship may be complicated in adolescents, however. Booth and colleagues (2003) found that low testosterone was related to depressed mood only when parent-child relationships were poor in both boys and girls. High testosterone levels appeared protective against depressed mood regardless of parent-child relationships. If high testosterone levels are related to depressed mood, a more extreme group, such as subsets of early maturing adolescents, may have been necessary to observe the full U-shaped function.

Finally, as might be expected from an outcome like mood swings, it is possible that absolute levels of hormones matter less than the variability in hormone values (Buchanan et al., 1992). Studies in cycling adult women show variations in positive and negative mood states, and these mood changes varied by the age of the woman. Adolescent girls may be particularly prone to such mood swings for two reasons. Their cycles are often irregular so their moods may be less predictable than older women. Adolescent girls may also be particularly sensitive to small changes in hormone concentrations because the negative feedback properties of steroid hormones have not sufficiently matured (Buchanan et al., 1992). Juvenile girls have few estrogen receptors, but puberty marks the time when many areas will begin to express estrogen and androgen receptors. Estrogen is a very powerful hormone, often with biphasic properties. It is possible that small changes in estrogen levels in early puberty will exert an exponentially larger effect on mood than larger changes might in an older woman. This type of model is supported in postmenopausal women (Rubinow et al., 2002) and by at least one study in adolescents. Brooks-Gunn and Warren (1989) found that depressive affect increased as estrogen levels quickly rose during girls' earliest pubertal stages. Thus, rapidly rising estrogen levels after the onset of puberty may be a hormonal contribution to adolescent moodiness (Buchanan et al., 1992). This later model is not at odds with the curvilinear model described above, nor does it contradict the observation that these hormones enhance mood. Though girls experience mood swings as the gonadal axis turns on for the first time, it is still unclear whether negative mood is experienced when estrogen is highest or lowest. More research is needed which directly measures variability in hormones and moods using frequent and adequate measures of both in order to uncover the nature of this paradox.

6.4] The Biological Underpinnings of Social and Peer Relationships is Different in Adolescent Boys and Girls

Adolescence marks a shift in their social lives from activities and interests that center on the family, toward more peer-directed activities. Adolescents spend one third of their waking hours with peers and only 8% with adults (Spear, 2000). Adolescents in less involved and cohesive families are more likely to be influenced by peers than adolescents in warm, supportive families (Steinberg & Morris, 2001). Children experience the deleterious consequences of family stressors most profoundly, but adolescents are more influenced by negative life events occurring in the peer and family domains, especially girls (Rudolph & Hammen, 1999). That peer victimization and rejection are experienced by many adolescents is particularly disheartening because of the negative consequences of these experiences (Steinberg & Morris, 2001). Some of these consequences include biological alterations in stress reactivity (Stroud, Salavey, & Epel, 2002). Nonetheless, it must be mentioned that peer victimization is not limited to adolescence but rather often begins in childhood (Schwartz, Dodge, Pettit, & Bates, 1997). It is notable that the social behavior of adolescents differs qualitatively, as well as quantitatively from that of children (Spear, 2000). Primate and human adolescents spend less time engaged in play behavior and more time expressing affiliative and bonding behaviors with same- and opposite-sex peers. Compared to childhood friends, adolescent friendships are marked by more intimate and supportive communication with like-minded agemates than during childhood (Steinberg & Morris, 2001). These types of social changes have a long history of hormonal influences.

The *tend and befriend* response describes a recent theory on the female response to stress (Taylor et al., 2000). Briefly, it suggests that females do not often respond to stress in the typical *fight or flight* manner which was based almost entirely on studies in men because they would often be compromised by pregnancy, lactation or young children (Selye, 1976). Instead, they tend toward their offspring and socially bond with other females. The female response to stress then first emphasizes social connection to children such that hormonally and pheromonally women find infants attractive (Fleming, Ruble, Kreiger, & Wong, 1997; Fleming et al., 1993; Fleming, Steiner, & Corter, 1997). Second, piggybacking on this response to infants, women find the companionship of other females rewarding. Studies in prairie voles suggest that following activation of the HPA axis, females show enhanced expression of social behavior and bonding with infants. These positive social behaviors then reduce the stress response in part by causing the release of oxytocin which induces feelings of relaxation (Carter, 1998). Oxytocin is a large peptide hormone released centrally into the brain in areas related to social information processing (Insel & Fernald, 2004) and the reward circuitry in the brain (Insel, 2003).

Where do adolescents fit in this model? Oxytocin does not show drastic increases at puberty, but estrogen rises in females at pubertal onset. Estrogen facilitates the effects of oxytocin in the social neurocircuitry; after puberty, girls are more likely to find social interactions rewarding. At least in many animals, females do not find interacting with infants rewarding until after puberty (Carter, 1998).

Studies in humans show more liberal responses to infants, but early breast development, under estrogenic control, encourages females to interest in infants and feminine behavior (Brooks-Gunn & Warren, 1988). Also, estrogen administration in hypogonadal females enhances feelings of romantic appeal and close friendships (Schwab et al., 2001). This model helps explain why adolescence mark the first stage when girls feel intense emotions about their peers and friendships take on heightened importance (Carter & Keverne, 2002). Thus, adolescents may be an important developmental stage leading to the establishment of social behavior and pair bonding (Nelson et al., 2005).

Adolescent males present a different view. Oxytocin is not as important in males as vasopressin, a similar neuropeptide centrally released in the brain which likewise encourages social attachment and pair bonding (Insel, Winslow, Wang, & Young, 1998). However, testosterone levels suppresses the release of oxytocin and vasopressin so the tend and befriend response is possible in males but is relatively diminished compared to females (Geary & Flinn, 2002). This renders flexibility to the biological activity surrounding male social bonding and allows bonding to be more contextually-dependent than in females (Taylor et al., 2002). This should not be taken as evidence that males do not invest in friendships or peer relations (Benenson & Christakos, 2003). Rather, the endocrine basis of male friendships entail more than positive social interactions.

Testosterone is implicated in adolescent boys' ability to maintain social dominance and competitive peer relations. Boys with high testosterone are perceived as socially dominant by unfamiliar peers (Schaal et al., 1996) especially when they have larger body mass (Tremblay et al., 1998). An interesting biosocial relationship has also been revealed. Boys with nondeviant peers who have high testosterone have leadership qualities and are perceived as popular by their peers while boys with high testosterone with deviant peers are more deviant themselves (Rowe, Maughan, Worthman, Costello, & Angold, 2004). This later finding supports a model implicating testosterone's role in maintaining social dominance as well as the idea that the biological basis of social interactions is often context-dependent in males (Taylor et al., 2002).

A final note on the biology of social behavior deserves mention. I have referred to 'pair bonding' throughout, without much mention of what pair bonding entails. This developmental stage is often marked by adolescents' first romantic relationship (Steinberg & Morris, 2001). Much of the literature on social behavior and hormones, especially the animal literature, involves the activation of circuitry devoted to sexual behavior (Romeo, 2003). This literature emphasizes that hormones are necessary to activate circuitry devoted to male and female sexuality, but once individuals gain sexual experience, hormones are no longer necessary (Hull, Meisel, & Sachs, 2002). Occasionally, stronger findings are reported in females because small changes in testosterone can exert a powerful drive on female sexuality whereas most males are well beyond the threshold permitting sexual behavior (Blaustein & Erskine, 2002). Although testosterone is intuitively related to sexual behavior, estrogen and DHEA likewise exert effects on sexual behavior (Finkelstein et al., 1998; McClintock & Herdt, 1996). Interestingly, sexual behavior

during puberty is one of the few arenas in which organizational influences of steroid hormones are generated after early postnatal life (Sisk & Foster, 2004). The hormonal rise at puberty and resultant sexual behaviors permanently alter the adolescent brain. Nonetheless, a review of the sexuality literature is beyond the scope of this review. In sum, hormones are strongly implicated in the onset and maintenance of social behavior. This strong assertion must be qualified because hormonal actions are frequently context-specific and -dependent.

6.5] Parent-Child Conflict Surprisingly Understudied

Adolescence is not only marked by a preference for interaction with peers, it is also marked by rising hostility toward parents, increased parent-child conflict, and less closeness with parents than during childhood (Steinberg, 2000). This is especially troublesome since parent-child relationships are powerful buffers against the possible deleterious consequences of negative peer interactions (Boyce & Ellis, in press). Very little evidence is available to guide further understanding of parent-child conflict. Holmbeck and Hill (1991) found that girls increased conflictual engagements with their mothers shortly after menarche, and this was received with emotional distancing and withdrawal of positive affect in the dyad within the first few months after menarche. Fathers were the recipients of conflict from both the mother and daughter and their attempts to re-establish positive relations were rejected by both women. Only one study has included hormonal measures. Strong and Dabbs (2002) found that testosterone was associated with low parental attachment, though their measures of attachment were not ideal and the age range included was younger than many other studies. Clearly, more research is needed on this topic to understand the neuroendocrinology of parent-child conflict.

6.6] Hormones Help Self-Esteem, But Body Fat Hinders Body Image

It is not surprising that self- and body-image change during pubertal development since this life stage is characterized by the greatest period of growth outside of fetal and early postnatal life. Self-esteem is stable during adolescence, perhaps even increasing across time, yet self esteem fluctuates daily in early adolescence (Steinberg & Morris, 2001). There is a reliable gender difference in body-image: girls frequently experiencing a decline in body image as they accumulate more adipose tissue and have a harder time maintaining an unrealistic ideal weight. Estrogen and leptin both facilitate the accumulation of a female-typical fat distribution. Boys, on the other hand, more frequently develop increased musculature that puts them closer to their ideal body image (Abraham & O'Dea, 2001; O'Dea & Abraham, 1995; O'Dea & Abraham, 1999a, , 1999b, , 2000). Testosterone and DHEA both facilitate this increased muscle mass and linear growth. Consequently, much of the literature on body image has centered on girls.

Pubertal development is not a single event, so developmental asynchronies between breast, pubic hair, linear growth and menarche can individually have different implications for changing body image. Breast development is a clearly observable event signifying sexual maturation (Brooks-Gunn & Warren, 1988). Although the authors thought that breast development would result in declining body image, this investigation showed that breast development led to increased

body satisfaction and more positive peer relations whereas menarche led to decreased body satisfaction and more self-conscious feelings (Brooks-Gunn & Warren, 1988). A similar longitudinal investigation showed that the rate of breast development and pituitary hormones have independent effects on body image, with faster increases in breast development signifying greater body satisfaction (Slap, Khalid, Paikoff, & Brooks-Gunn, 1994). A longitudinal study from a different group found consistent increases in self image across one year. Increases in body image were related to genital stage rather than age, implicating possible hormonal involvement. These findings are in keeping with ideas that breast development signals maturity in girls, but not with models that emphasize faster rates of development as risk factors for poor body image. Another study focused on weight gain rather than breast development because girls normatively gain about 25 pounds across the pubertal transition; this weight gain is often cited by girls as a cause of poor body image (Graber, Brooks-Gunn, & Warren, 1999). A very large study of girls found that early pubertal timing and greater susceptibility to gender intensification (the importance of the female figure) led to poor body satisfaction (Wichstrom, 1999).

Finally, other studies focus on body image and eating behaviors that begin to indicate risk, though not all girls will develop eating disorders. The topic of eating disorders is beyond this review, but some mention of subclinical eating problems must be made since about 20% of girls will develop some eating problems (Brooks-Gunn, Graber, & Paikoff, 1994). Chronic eating problems are linked with pubertal events, but often do not develop until girls are nearly finished developing. Girls did not experience a decline in self-esteem until Tanner Stage 5 (Huerta & Brizuela-Gamino, 2002), and eating disturbances are not often evident until after menarche, a rather late pubertal event (Abraham & O'Dea, 2001; O'Dea & Abraham, 1995; O'Dea & Abraham, 1999a, , 1999b, , 2000). Disordered eating is particularly common in high achieving\ anxious girls, lending further support to the idea that declining body image is related to body fat accumulation taking girls further away from their ideal body shape. Eating problems can also emerge later, when girls transition away from the home, especially when they come from enmeshed, overprotective, rigid families (Brooks-Gunn et al., 1994).

Models for body image changes in adolescence, then, emphasize that biological changes are likely a mediator for changes in body image, rather than a direct cause for declining body satisfaction. If anything, higher estrogen and testosterone contribute to satisfaction, well-being, and positive body image. Growing breasts also are greeted with satisfaction. Accumulating body fat, in part through biological actions of estrogen and leptin, triggers body dissatisfaction and poor self-image. Cultural forces combined with biological changes are proximal causes of declining body image. A host of psychological effects also result from the social stigma of fat accumulation in our culture (Brooks-Gunn et al., 1994; Cruess et al., 2000; Wichstrom, 1999). One final, perhaps more personal, note about body image is warranted as long as I'm citing popular culture. Body fat accumulation is not the only experience that adolescent girls and boys experience. Advertisements featuring Jennifer Love Hewitt or Mena Suvari tell us that acne is one of the worse scourges of puberty. Evolutionary models emphasize the importance of clear skin in

conveying immune and reproductive health in both males and females (Rhodes, Chan, Zebrowitz, & Simmons, 2003). Also, one of the main reasons for women with polycystic ovary syndrome to report poor self-esteem is due to acne (Pfeffer et al., 1989). Skin changes and body odor are caused by gradual increases in adrenal androgens and testosterone. It may behoove us to broaden understanding of puberty to include peripheral changes other than Tanner Staging.

6.7] Organizing/Activating Hormones Help Adolescents Form an Identity

Steinberg describes adolescence as a time when individuals explore their psychological selves and discover who they really are (Steinberg & Morris, 2001). This process appears particularly cognitive, but some evidence has described hormonal links with identity formation. This does not necessarily include sexual identity, as the evidence for organizational influences of hormones on sexual identity have been equivocal and the controversy around this topic is heated (Migeon & Wisniewski, 1998).

The identity challenge for early adolescents may be to accept their growing and changing body; mid-adolescence may be to experiment with emotional and physical separations from the family; late adolescence then focuses on establishing an identity of one's own with romantic partners and friends (Remschmidt, 1994). One interesting role for pubertal maturation in identity formation may be to encourage adolescents down one pathway or another. As mentioned earlier, girls who show their growth spurt first rate career importance highly, whereas girls who show breast development first are more likely to have intensified gender roles and rate marriage and children highly (Brooks-Gunn & Warren, 1988). Thus the nature of the experience of puberty may influence the identity and social roles that adolescents invest in as adults. A provocative study of the organizational influences of prenatal androgen exposure in girls with congenital adrenal hyperplasia revealed preferences for careers and activities that are more male-typical (Berenbaum, 1999). These girls typically fall halfway between their normal sisters and brothers, allowing ample room for both biological and social forces to take effect. Activational effects may also play a role with identity formation. Hypogonadal adolescents given testosterone and estrogen to boys and girls, respectively, rated themselves with more perceived job competence, with better close friendships in females and with better athletic abilities in males (Schwab et al., 2001). High testosterone is related to low occupational achievement and unemployment, however, so some functions of hormones on identity formation may not be on a cognitive but rather a motivational level (Dabbs, 1992). These findings support the notion that many aspects of identity formation mature with psychological and cognitive functions, but that the initial challenge of identity formation may have its basis in pubertal maturation (Sinkkonen, Anttila, & Siimes, 1998). Events subsequent to pubertal maturation may thereby be influenced by how the adolescent navigates that early life stage.

6.8] Intuitive Link with Aggression Simplistic, But Hormones are Key

Aggressive behavior does not appear at adolescence. Rather antecedents can be seen early in childhood (Tremblay et al., 2004). Nevertheless, aggressive behavior is a hallmark symptom of problems that are often adolescent-limited, such as

violence, delinquency, and conduct disorder, so it is worthwhile to consider the hormonal contribution to aggression. Aggressive behavior peaks in adolescence, with some behaviors pointedly directed toward adult males (Spear, 2000). Escalating symptoms of the aggressive child may also be exaggerated by permissive hormonal factors. Much of this literature is on testosterone in boys. Aggression is reliably different in boys and girls (Zahn-Waxler et al., 2006).

A developmental view on the trajectories of aggressive behavior is in keeping with the *trouble with testosterone* (Sapolsky, 1997). Testosterone is frequently on the scene when aggression levels soar. In seasonal breeders, testosterone levels peak when intermale fighting is most frequent; testosterone and aggression are higher in males than females; testosterone and aggression peak in adolescence. But the trouble with testosterone is that it doesn't cause aggression, but rather exaggerates the aggression that was already present. Thus, the aggressive child may become the violent or delinquent adolescent when his testosterone levels rise at puberty, but the aggressive impulses likely present (but perhaps not acted upon) before the rise in testosterone. One early longitudinal study in 15-17 year old boys supports this model. High testosterone led to an increased readiness to respond to provocation, but testosterone was unrelated to unprovoked aggression (Olweus, Mattsson, Schalling, & Low, 1980, , 1988). That is, testosterone facilitated an aggressive response to a situation which likely called for aggression. Nevertheless, a powerful hormone replacement study in hypogonadal boys did indicate that moderate doses of testosterone caused substantial (~20%) increases in aggressive impulses, physical aggression against peers and physical aggression against adults. These effects were not evident at low or high doses of testosterone, suggesting that testosterone may contribute to aggression when it is rapidly rising.

Another trouble with testosterone is that it may be directly linked with social dominance, and consequently indirectly linked with aggression (Mazur & Booth, 1998). A socially dominant individual may respond aggressively if they are in a situation where their social status must be maintained. This may explain why many studies fail to find links between testosterone and aggression (Constantino et al., 1993; Halpern, Udry, Campbell, & Suchindran, 1993). Schaal and colleagues (1996) found that adolescent boys perceived as socially dominant had higher testosterone levels than less socially dominant boys, and physical aggression was actually associated with low testosterone. Tremblay and colleagues (1998) likewise found that testosterone in adolescents predicted social dominance but not physical aggression. This finding suggests that some of the effects of testosterone on muscular physical development may indirectly permit higher levels of aggression in adolescents. Interestingly, this model also holds for women, though as a population they have much lower testosterone levels than men (Dabbs & Dabbs, 2000).

Other hormones also may contribute to aggression in adolescence, though the biosocial models are not yet sophisticated. High estrogen levels were associated with aggressive behavior one year later in girls (Brooks-Gunn et al., 1994). Higher estrogen and androstenedione levels were associated with more aggressive behavior in girls, particularly defiant and explosive aggression (Inoff-Germain et al., 1988). In hypogonadal girls receiving estrogen to stimulate pubertal maturation, low and mid

doses of estrogen caused a 48% and 40% increase in aggressive impulses, and a 28% and 31% increase in physical aggression against peers and adults respectively. These results provide substantial support for estrogen contributing to aggression. The fact that aggression did not continue to rise at a high dose, however, suggests a threshold or acclimation effect (Finkelstein et al., 1997).

Few studies have explored relationships between DHEA and aggression, but the findings are promising. Highly reactive boys had low DHEA levels (Inoff-Germain et al., 1988), and girls with low DHEA and had negative interactions with friends were more aggressive than girls with high DHEA (Brooks-Gunn & Warren, 1989). Conversely, high DHEAS levels were related to the intensity of aggression, although it is not surprising that these studies did not converge as these subjects were younger and had serious behavior problems (van Goozen, Matthys, Cohen-Kettenis, Thijssen, & van Engeland, 1998).

In sum, a provocative double-blind placebo controlled study clearly implicated rising testosterone and estrogen levels in the adolescent rise in aggression in boys and girls. Nonetheless, correlational studies suggest social dominance is more directly related to testosterone. Adolescents with low DHEA levels appear more aggressive than adolescents with high DHEA, particularly when they experience negative peer interactions.

6.9] Adolescents are Risk Takers

Spear (2000) aptly wrote that *adolescents are risk takers* to describe the adolescent rise in risk taking behavior. This model is readily apparent with humans, in which 80% of 11 and a half to fifteen year olds exhibited problem behaviors related to risk taking and norm violating behavior (Spear, 2000). It is also interesting that nonhuman primates are also known risk takers, perhaps because occasionally risks can increase ones abilities and provide access resources that might otherwise have been unavailable (Sapolsky, 1997). For humans, risk taking behavior can convey benefits for popularity, friendships, social acceptance, and opposite-sex relationships; adolescents who do not take risks are boring (Dishion, Andrews, & Crosby, 1995). Although normative, risk taking can present developmental snares. Moffitt's original taxonomy for adolescent-limited and lifecourse persistent antisocial behavior predicted that some adolescents would engage in risky behavior which would subside when they reached adulthood (Moffitt, 1993). What they found when they followed up these youth until the age of 26, instead, was that a significant percentage of adolescent-limited risk takers were still engaging in antisocial behavior (Moffitt, Caspi, Harrington, & Milne, 2002). Rather than changing their terminology, however, Moffitt insulted young people everywhere by suggesting that perhaps these subjects were still 'adolescents' at the age of 26, because they had not yet taken on adult roles and responsibilities (Dahl, 2004). A basic understanding of risky behavior may be necessary to understand how such behaviors can become problematic. The biological basis for this later component of adolescence will be described in a later section as there is some evidence that risk taking behavior and delinquency or drug addiction have different underlying biological contributions (Moffitt & Caspi, 2001).

Dahl's (2004) model emphasizes the natural tendency for adolescents to take risks and implicates the emotion circuitry in the brain, which develops along the pubertal trajectory, in igniting the passions of adolescents. Justice to this model cannot be done here, but I should re-emphasize that the emotion circuitry central to this model is highly influenced by sex steroid hormones (Nelson et al., 2005). There is ample reason to suppose that hormonal activation of the reward circuitry in the brain may be one biological contribution to risk taking behavior in adolescents.

A handful of studies have examined risk taking behavior. Warren and Brooks-Gunn (1989) found that impulse control decreased and the increased as estrogen and pubertal stages advanced. Susman and colleagues (1987) found that higher levels of androstenedione in boys were related to more acting-out behaviors. An intriguing biosocial role for testosterone has also been explored. High testosterone was related to more risky behavior in both boys and girls, but only in those adolescents who had poor quality relationships with their mothers and fathers (Booth et al., 2003). These studies point to a role for steroid hormones even within the normative risky behaviors evident in the majority of adolescents. Most research in this area, however, has targeted adolescents with extreme behavior problems and emotional disorders (reviewed below).

6.10] Summary and Integration

Adolescence marks a life stage characterized by changing hormones and changing behaviors. Some behavioral changes in adolescence can be linked directly or indirectly to pubertal changes. Many of the hormones investigated in other lifestyles have likewise been explored in adolescence with paradoxical results. Hormones help us feel better, remember better, metabolize better, and interact better with peers. Why then should adolescence be a risky time? The answer is not yet known, but clearly a model more complex than a direct hormone-behavior relationship is necessary.

Eating behavior increases in adolescence, in part because of metabolic hormones like leptin. Adolescents have an increased physiological need for sleep, a biological propensity for staying up late, and a culture which requires early morning attendance at high school. Although moodiness is most intuitively related to pubertal hormones, very few studies have actually studied mood swings. Hormones often enhance mood, but pubertal maturation may mark a difficult stage in which adolescents must acclimate to their new biological state. This is clearly an area in need of high quality research with repeated measures of mood and hormones so that variability in biology and behavior can be adequately measured. Adolescent interactions with peers is more important than ever before. At this lifestage, gonadal hormones facilitate activity in the reward circuitry of the brain when adolescents connect socially, raising one scientist to speculate that we are "addicted to love". Social relationships are powerful, intense and sometimes fragile. They can serve as buffers against life stress, as the tend and befriend theory suggests, or they can be detrimental if they serve as sources of stress. The hormonal changes in the adolescent brain favor female interactions with infants and other females. Social relationships for boys are more context-dependent and help boys maintaining social dominance. Parent child conflict and a distancing from the family are hallmarks of

adolescence, but it has not been sufficiently studied in relation to pubertal timing, maturation or hormonal change. More research is clearly needed, especially since studies examining broad outcomes indicate the early and concurrent family cohesion as a powerful stress buffer. Pubertal maturation, breast development, and hormonal change are consistently linked with positive self image, consistent with the idea that they signal maturation. The accumulation of body fat and self consciousness around menarche, however, leads to poorer self image in girls. Adolescent experience with acne is an area in need of research. This appears to be a rather late event, occurring after menarche or when girls transition away from home, so cultural and psychosocial forces are likely implicated rather than pubertal maturation. Both organizational and activational hormonal changes have been associated with identity formation in adolescents, in part through maturation timing and synchrony. This is one of the few studies to test a synchrony model. Although the intuitive link between hormones and aggression is obvious and one study supplied clear experimental evidence for a relation, in truth social dominance may be more tightly linked with testosterone than aggression. Testosterone more likely plays a permissive role. It doesn't cause aggression, as not all adolescents experience problems with aggressive impulses, but rather testosterone exaggerates the aggression that is already there. This helps explain why there is developmental continuity in aggression from childhood through adolescence. A model outlined by Dahl views adolescents as risk takers and the neurocircuitry that is involved with these drives is activated by hormones and matures with pubertal events.

A general theme with all these behaviors is that a direct relationship between hormones and behaviors is relatively rare. Models that emphasize adolescents getting accustomed to their new biology or hormones exerting a permissive or exaggerating effect on the expressed behavior are more sophisticated. These models should also be favored as they can account for the fact that adolescents may show these behavioral changes, but adults do not. If there is a direct relationship between hormones and behavior, then most adults would be moody, aggressive, irritable risk-takers who sleep all day. Models that emphasize timing, duration, synchrony and context should be favored. Some provocative studies described below emphasize that when more than one of these factors is offset or when adolescents also experience extant life stressors, behavior problems in the clinical range may result. If not, most adolescents will navigate this developmental stage with appropriate adult roles and responsibilities.

7. Adolescent Disordered Behavior

This section will complete the circle on adolescent behavior and the pubertal transition by emphasizing biological changes that contribute to adolescent vulnerabilities to psychopathology. Understanding vulnerability helps us understand both normative and atypical development. A biosocial perspective is particularly useful for understanding psychopathology because most adolescents experience biological change but only a subset has major problems. Social contextual factors must also be implicated. Internalizing, externalizing and drug abuse are three psychological problems that typically emerge in adolescents.

7.1] Hormonal and Pubertal Status and Timing Are Risks for Internalizing Behavior Problems

The term *internalizing behavior problems* describes a broad series of symptoms that relate to disturbances in introjective emotions and moods such as guilt, fear and worry (Zahn-Waxler, Klimes-Dougan, & Slattery, 2000), and often has been operationalized using measures of depressive and anxiety symptoms (Achenbach, 1991a, , 1991b) or as psychiatric symptoms of anxiety and depression (Fisher et al., 1993; Schwab-Stone et al., 1993; Shaffer, Fisher, Lucas, Dulcan, & Schwab-Stone, 2000; Shaffer, Fisher, Piacentini, Schwab-Stone, & Wicks, 1989; Shaffer et al., 1993).

Internalizing behavior symptoms are common in children and adolescents, but relatively few children in the general population express these behaviors in the clinical range. The incidence of internalizing disorders varies by age. The age of onset of anxiety disorders is in middle childhood (Barrios & Hartmann, 1988). In adolescence, anxiety disorders were prevalent in 7.5%, 10.7%, and 19.7% of 11, 15, and 18 year olds, while depressive disorders were prevalent in 1.8%, 4.2% and 18% of 11, 15, and 18 year olds from the general population, respectively (Kovacs & Devlin, 1998). Throughout childhood, boys and girls have similar prevalence rates of anxiety and depression, but adolescent females are more than twice as likely than are adolescent males to develop internalizing problems (Mash & Terdal, 1988; Wilhelm, Roy, Mitchell, Brownhill, & Oarker, 2002; Zahn-Waxler et al., 2000). Depression and anxiety are largely stable from adolescence to adulthood (Kazdin, 1988; Zahn-Waxler et al., 2000). Girls with depression or anxiety problems at age 11 were 6.2 times more likely to have an internalizing disorder at age 15 than were girls without internalizing disorders (McGee, Feehan, Williams, & Anderson, 1992).

Because female adolescents are at heightened risk for developing internalizing disorders, an expansive body of literature has examined depression in girls. A very large study of girls in Australia found that menarcheal status was an important transition point in girls risk for depression, with menarcheal status contributing a 50% higher risk for depression. Indeed, menarcheal status, even when controlling for age, was a better predictor for divorce than perceived stress, parental divorce and parental education achievement (Patton et al., 1996). Another large sample study noted that depression, anxiety and poor self image increased as girls advanced through the tanner stages and was particularly notable by Tanner stage 5 (Huerta & Brizuela-Gamino, 2002). A smaller study found that depressed adolescents reported more negative and less positive affect, but this effect interacted with both age and pubertal status. Depressed girls who were mid-to-late pubertal reported sharply most elevated negative affect (Forbes, Williamson, Ryan, & Dahl, 2004). Finally, a recent review of the literature on depression in adolescents concluded that pubertal status was a better predictor of depression than the timing of puberty when predicting clinical level depression (Kessler, Avenevoli, & Ries Merikangas, 2001), based largely on Patton's study.

My read of the literature, however, suggests that both timing and status may be important. Wichstrom (1999) proposed a provocative model in which pubertal status correlates with depressed mood in early adolescent girls frequently. When

this is combined with early maturation compared to one's peers, clinical level depression may result. Part of this depressed affect may result from girls moving further away from their ideal body type as body fat accumulates, and this effect may be especially pronounced in girls whose gender roles intensify the most across the adolescent period. That pubertal timing can influence how much girl's femininity intensifies suggests this may be a reciprocal model. In a very large Norwegian sample, they found surprisingly solid empirical support for this model. Another longitudinal study likewise found that girl's depression began to emerge at the age of 13 or 14 and that initial pubertal status but not subsequent status was related to subsequent depressive symptoms (Ge, Conger, & Elder, 2001). They also found that the timing of menarche was related to depressive symptoms with early maturers most at risk. When also combined with life stressors, early maturers were the most likely to succumb to depression. Finally, this depression was most persistent in the early maturing depressed girls compared to those on-time or late-maturing girls who at one time were depressed. These results suggest that both status and timing are important for the prediction of depression in adolescent girls, but that the effects of timing may be more long lasting than status alone (Ge et al., 2001).

That both pubertal status and timing play a role in the onset and persistence of depression suggest both contextual and hormonal changes may be at work despite suggestion of the unimportance of pubertal events (Hankin & Abramson, 1999). As reviewed above, this literature is complicated because hormones as a general rule enhance mood and have antidepressant actions (McEwen, 2001). Nonetheless, hormonal changes at pubertal onset may increase the risk for depression in some individuals because biological transitions are a time of increased vulnerability for some individuals (Dorn & Chrousos, 1997). Adolescents must acclimate to this new hormonal, physical and social status. Vulnerabilities may result when life stressors, negative events, or physiological dyssynchronies combine with hormonal changes (Hayward & Sanborn, 2002). As reviewed by Steiner and colleagues (1992), the fluctuation of estrogen across most phases of the reproductive lifecycle show increased prevalence of depression in women. These vulnerabilities are evident when estrogen rises and falls, suggesting cyclicity and acclimation may play a part, but not in all women. Further, these changes in estrogen levels also change how other neurotransmitters and steroids interact in the brain. Changes in HPA axis activity may be evident when girls experience life stressors, and the HPA and HPG axis heavily interact (Viau, 2002). Consequently, the combination of observing HPA and HPG axis changes when girls experience concurrent pubertal maturation and negative life stressors will probably be the best model to account for the adolescent rise in depression (Parry & Newton, 2001).

Other hormones also may contribute to adolescent depression. Depression is a frequent complaint in girls with polycystic ovary syndrome who are exposed to excessive testosterone levels (Pfeffer et al., 1989). Although there was no effect of testosterone in the girls, our investigation in at risk boys showed low testosterone and flat diurnal slopes were associated with more anxiety and depression symptoms (Granger et al., 2003). At least one study has found that the pubertal rise in testosterone and estrogen explains the association between pubertal status and depression in adolescents (Angold, Costello, Erkanli, & Worthman, 1999).

Goodyer's studies on depressed adolescents reveal that DHEA is a relatively reliable predictor of subsequent first-episode major depression (Goodyer, Herbert, Tamplin, & Altham, 2000) and that adolescents who were persistently depressed had an elevated cortisol/DHEA ratio at study entry (Goodyer, Herbert, & Altham, 1998; Goodyer, Herbert, & Tamplin, 2003). Nevertheless, there is some criticism of Goodyer's conclusion that DHEA or the cortisol/DHEA ratio may be predictive of later depressive disorders since the specificity of a high cortisol/DHEA ratio is rather poor (Angold, 2003). Collectively, these studies suggest that the status, timing, and hormonal events of pubertal maturation can contribute, but does not cause, depression in adolescents. The addition of a negative life stressor may place adolescents more at risk for depression because they are also experience large biological changes. When these pubertal changes are early, adolescent girls at most at risk for persistent depression. Little is known about these events in boys, so this is an obvious area in need of research.

7.2] Social Context Can Intensify or Buffer Adolescents from Hormone-Related Externalizing Behavior Problems

Externalizing behavior disorders are a broadly defined category that refers to a continuum of behavior problems described as disinhibited, undercontrolled, undersocialized and aggressive (Kovacs & Devlin, 1998). Externalizing behavior includes a pattern of persistent and repeated violations of social rules and the rights of others (American Psychiatric Association, 1994), such as aggression toward people and animals, destruction of property, deceitfulness and theft, and an emotional profile that includes impulsivity, hostility, and a lack of empathy. The Diagnostic Interview Schedule for Children includes conduct disorder (CD), oppositional defiant disorder (ODD) and attention deficit hyperactive disorder (ADHD) (Fisher et al., 1993; Schwab-Stone et al., 1993; Shaffer et al., 2000; Shaffer et al., 1989; Shaffer et al., 1993). Lewisohn and colleagues (1993) report prevalence of externalizing disorders at 1.81% in 14 – 18 year olds, but others report prevalence at 9.1%, 11.9% and 5.5% in 11, 15, and 18 year olds (Kovacs & Devlin, 1998). Across 21 general population studies, ADHD occurs in 3.19 % and CD/ ODD occurs in 7.18% of children on average (Angold, Costello, & Erkanli, 1999).

The age of onset of externalizing behavior is the center of much discussion, with differences in risk factors (e.g., parental, social, temperamental, and neurobiological factors, Moffitt & Caspi, 2001) and lifetime trajectories (e.g., severity and persistence of crime, Moffitt et al., 2002) expected for youth who engage in problem behavior in childhood versus adolescence (Campbell, Shaw, & Gilliom, 2000). Nevertheless, youth who engage in delinquent acts at a normative level during adolescents may continue to encounter problems in early adulthood (Dishion, 2000; Dishion & Owen, 2002; Moffitt et al., 2002). Males with life-course persistent antisocial behavior account for 53% of violent offenses though they comprise 10% of the total population; 'adolescent-limited' delinquents account for 29% of violent offenses, 45% of drug offenses, 34% of rule offenses and 54% of property offenses though they comprise only 26% of the total population.

The stability of externalizing behaviors across time is high (Achenbach, McConaughy, & Howell, 1987), and likely to increase across the adolescent years.

As the types of behaviors expressed go from mild to moderate (e.g., risky or truant behavior) to severe (e.g., delinquent and criminal acts), the likelihood that they will desist decreases and the cost to the general public increases (Moffitt & Caspi, 2001; Moffitt et al., 2002). A big challenge for research on externalizing behavior is predicting when normative behaviors will escalate to truancy, delinquency and violent juvenile offending (Loeber & Farrington, 2000). One quarter to one half of children who engage in disruptive acts go on to engage in more delinquent acts; one-third to two-thirds of children who engage in delinquent acts escalate to serious delinquency; and 40 – 60% of seriously delinquent youth become chronic lifetime offenders (Loeber & Farrington, 2000).

Externalizing behaviors are more common and more stable in males than females. Sex differences in externalizing behavior emerge as early as two years old, with male adolescents engaging in externalizing behavior 1.5 (Moffitt & Caspi, 2001) to three times (Loeber & Farrington, 2000) as much as females.

Early maturation appears to be a risk factor for externalizing behavior problems for both boys and girls, through similar mechanisms. Early maturation increased delinquent behavior in a large sample of girls, and slower pubertal change across two years was related to more problem behavior (Laitinen-Krispijn, Van der Ende, Hazebroek-Kampschreur, & Verhulst, 1999). Although this sample was normative, the large sample size suggests a substantial subset were engaged in clinical level delinquency. Early maturing boys across three ethnic groups also engaged in more violent and nonviolent delinquent behavior in a large sample of boys. Another study looked at a large sample of African American children and found that early maturing boys and girls were more likely to affiliate with deviant peers than later-maturers and to have externalizing problems when they came from harsh and inconsistent parents (Ge, Brody, Conger, Simons, & Murry, 2002). These studies collectively suggest that early maturing boys and girls may be at heightened risk for externalizing behavior problems because their physical form signifies maturity to older, deviant peers but they may not yet hold the emotional maturity to affiliate with prosocial peers.

Is externalizing behavior related to hormonal levels? Some evidence for high testosterone relations exist. In an incarcerated population, men with high testosterone had committed more violent crimes, were judged more harshly by the parole board, and violated prison rules more often than those low in testosterone (Dabbs, 1991). In an older sample, delinquent youth had higher testosterone levels than college students (Banks & Dabbs, 1996). Testosterone levels were high in boys with externalizing behavior problems if they also had deviant peers (Rowe et al., 2004). In my own work, however, we found no relationship with externalizing behavior problems and testosterone in boys, but that boys with more attention problems had lower testosterone and shallower declines in testosterone across the day; by the afternoon, boys with attention problems would have higher testosterone levels than other boys (Granger et al., 2003). For girls, pubertal status masked an association between testosterone and externalizing behavior problems. More advanced girls had higher testosterone and shallow diurnal slope. When controlling for pubertal status, girls with more externalizing behavior problems displayed

steeper diurnal rhythms. This suggests that the diurnal rhythm of testosterone changes as girls mature, but when holding this developmental effect constant, girls with high morning testosterone and steep diurnal slopes are at risk for externalizing behavior problems (Granger et al., 2003). There are two possible explanations for the inconsistencies in the testosterone literature. First, high testosterone levels may contribute to externalizing behavior in certain contexts, but not others (Susman & Ponirakis, 1997). When these contexts facilitate social dominance, testosterone and delinquency may continue to rise. Another possibility is that testosterone rises in response to externalizing behavior. Testosterone levels rise in 'winners' and decline in 'losers' in response to competition in both males and females (Booth, Shelley, Mazur, Tharp, & Kittok, 1989). When contexts do not reward externalizing behavior, testosterone levels are expected to be low as we found in the 2003 study (Mazur & Booth, 1998). Adolescence may be a critical period to intervene. By the time they reach adulthood, aggressive and violent men consistently have higher testosterone levels presumably because their subcultures have rewarded such behavior (Raine, 2002).

Other hormones have also been investigated with externalizing behavior problems, though not as frequently. Van Goozen and colleagues found that boys with conduct disorder had higher DHEAS and androstenedione, but not different testosterone. Within the conduct disorder boys those who were more aggressive and delinquent had the highest DHEAS levels (van Goozen et al., 1998). This research group also found high DHEAS levels in children with ODD compared to normal controls or psychiatric controls, suggesting DHEAS is a relatively specific externalizing marker (van Goozen et al., 2000). Rising estrogen levels also predicted delinquent and aggressive behavior measured one year later (Brooks-Gunn et al., 1994). Collectively these results suggest that testosterone may be a marker, but not a cause, of externalizing behavior problems and may be useful as an indicator of behavior problems that are likely to persist. High DHEA and estrogen have been found in a few studies of externalizing youth, so clearly more research is needed on the hormonal correlates of externalizing behavior problems. The importance of developmental shifts in social contexts is underscored.

7.3] Permanent Alterations in Reward Circuitry Contribute to Drug Use

Some of the novelty-seeking and risk taking behavior of adolescents includes drug experimentation and use. Well over 50% of adolescents by their senior year have tried drugs, alcohol, and illegal substances; Over 25% of 8th graders have reported alcohol or drug use as well, suggesting use begins early (Spear, 2000). Some of this use is mere experimentation and adolescents are likely to desist. Yet pubertal changes and secondary sexual development can interact with socialization in the family and peer networks to predict drug abuse. Families characterized by conflict and lack of parental warmth may inadvertently encourage youth to disengage from the family and engage with deviant peers who encourage persistent drug use (Dawes et al., 2000). Thus, pubertal timing and family conflict display a biosocial interaction to predict initial drug use in adolescents. Adolescents, in particular, may proceed from drug experimentation to abuse faster than adults

(Dawes et al., 2000). This is in part modulated by the connection of the HPA and HPG axes (Dawes et al., 2000).

Why do adolescents develop drug addiction quickly? Dawes and colleagues' (2000) model suggests that maturational dyssynchrony in the timing and sequencing of hormonal, physical and social processes occurs in early adolescence which can change the homeostatic activity of the HPA and HPA axis resulting in altered activity in the brain reward mechanisms (Dawes et al., 2000). Low reward dependence is a risk for development of substance abuse disorders; adolescents as a group are high novelty-seekers and have low harm avoidance during puberty. But high risk youth from poor family backgrounds or with deviant peers are especially noted for high novelty seeking and low harm avoidance.

The brain is organized to find social stimuli rewarding. The same neurocircuitry and neurotransmitters that respond to drugs of abuse are implicated in the 'social' brain (Insel, 2003). That social salience changes dramatically after puberty may explain why adolescents are also at risk for drug abuse. Drugs of abuse may be co-opting the plasticity in the reward circuitry in part through activation by gonadal steroids (Keverne, 2004). It is interesting that this neurocircuitry is one of a few brain areas which show organizational influences by gonadal steroids occurring at puberty (rather than prenatally). This adolescent vulnerability to drug addiction may become entrenched in the adult because drug use has permanently altered the social brain. Consequently, it may be particularly difficult to change the neurocircuitry after drug addiction is established in the adolescent brain (Andersen, 2003).

Relations with hormones are equivocal. Testosterone levels were higher in adolescents who had recently smoked cigarettes and who had an earlier age of pubertal onset (Martin et al., 2001), but subjects at the time of testing were age 21. Another study found that adolescents at risk for substance abuse disorders had lower testosterone and dihydrotestosterone prior to a laboratory stressor (Dawes et al., 1999). Clearly, more research on the hormonal contribution to drugs of abuse is needed, especially if it can include brain activation information as well. Adolescents show many alterations in pharmaco-kinetic and -dynamic responses to many drugs (including pharmaceuticals). A full review of the adolescent propensity toward drug addiction has been conducted by Spear (2000).

7.4] Summary and Integration

It is unlikely that hormones or pubertal maturation will alone explain why some adolescents develop psychopathology. Hormones may operate as risks or protect against behavior problems depending on the family and peer interactions of the adolescent. Underlying biological vulnerabilities can be overridden by warm parental interactions, while associations with deviant peers and high hormones can result in a host of behavior problems. When adolescents also experience negative life events at the time of hormonal change, internalizing behavior problems may result. Biosocial models have been useful for advancing our understanding of adolescent vulnerability to psychopathology.

Puberty happened to the best of us. With the possible exception of J.M. Barrie, we all grow up sometime. Studies which center on individual differences in pubertal experiences are valuable for demonstrating the wide range of hormonal values that can accompany various adolescent behaviors and they have added greatly to our understanding of the complexity of the system, but a different research design may be necessary to understand the normative pubertal process and the points of vulnerability in this process which may contribute to behavior disorders. Knowing that a girl is 13 years old tells little about her pubertal maturation. Knowing that she is Tanner stage 3 tells more. Knowing that she comes from a conflictual single parent family tells even more about her likely developmental trajectory. But knowing that she has been maturing for the last two years and grew breasts rather quickly compared to her agetates and that her estrogen and leptin levels are very high tells us the most about her likelihood for getting depressed or developing an eating disorder. To have such knowledge requires longitudinal investigations that track juveniles through the pubertal transition frequently enough to permit monitoring of individual developmental trajectories. Only then will hormonal contributions to the development of psychopathology in adolescents be clarified.

That the effect of hormones on problem behavior is frequently context dependent raises an important point for interventions. Simplistic models suggest that our biology determined the kind of person we become. Growing empirical evidence does not support this view. Rather, high testosterone can contribute to prosocial behaviors in one context and antisocial behaviors in another; hormones can exaggerate aggression when the environment is permissive or have no effect when the environment is constrained. Adolescence is often a lifestage in which growing behavioral problems can become entrenched on a deleterious pathway, and remediation may be difficult in adults once the biological risk factors are set. Interventions aimed at changing our environment or social contexts may be more effective than interventions that try to change our biology. But one of the results of such interventions may actually be to change our hormonal risk factors (Fisher et al., 2000). More studies are necessary to clarify what types of social contexts encourage positive hormonal effects in adolescents.

8. Conclusion

This review has intended to provide background understanding of the influence of pubertal hormones on adolescence, with particular attention given to our knowledge about the variance in hormonal measures in individuals at risk for psychopathology. This research emphasizes that the organizational/ activational hypothesis holds implications for understanding how hormones influence the brain beyond secondary sexual maturation. It is clear that hormones and brain development change drastically at pubertal onset. A direct extrapolation of these biological events to behavioral change cannot be made. A developmental psychopathology framework helps us understand why biological and social factors place some adolescents at risk for behavior problems. This author looks forward to discussions which will address the implications of central and peripheral biological changes on our understanding of adolescent health and development.

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