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The Development of Psychotic Disorders in Adolescence: A potential role for hormones

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Abstract

The notion that adolescence is characterized by dramatic changes in behavior, and often by emotional upheaval, is widespread and longstanding in popular western culture. In recent decades, this notion has gained increasing support from empirical research showing that the peri- and post-pubertal developmental stages are associated with a significant rise in the rate of psychiatric symptoms and syndromes. As a result, interest in adolescent development has burgeoned among researchers focused on the origins of schizophrenia and other psychotic disorders. Two factors have fueled this trend: 1) increasing evidence from longitudinal research that adolescence is the modal period for the emergence of “prodromal” manifestations, or precursors of psychotic symptoms, and 2) the rapidly accumulating scientific findings on brain structural and functional changes occurring during adolescence and young adulthood. Further, gonadal and adrenal hormones are beginning to play a more prominent role in conceptualizations of adolescent brain development, as well as in the origins of psychiatric symptoms during this period (Walker and Bollini, 2002; Walker et al., 2008). In this paper, we begin by providing an overview of the nature and course of psychotic disorders during adolescence/young adulthood. We then turn to the role of hormones in modulating normal brain development, and the potential role they might play in the abnormal brain changes that characterize youth at clinical high-risk (CHR) for psychosis. The activational and organizational effects of hormones are explored, with a focus on how hormone-induced changes might be linked with neuropathological processes in the emergence of psychosis.

Keywords

psychosis; prodrome; puberty; adolescence; hypothalamic-pituitary-adrenal [HPA] axis; hypothalamic-pituitary-gonadal [HPG] axis; brain development

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Introduction

Schizophrenia and other psychotic disorders (e.g., schizoaffective disorders, and mood disorders with psychotic features) continue to be among the most serious and debilitating of all mental illnesses (Geller et al., 2000; Murray and Lopez, 1996; Wu et al., 2005). With the advent of antipsychotic medications, especially the atypical antipsychotic medications, the prognosis for patients has improved, and more are able to live in the general community. Nonetheless, most individuals diagnosed with a psychotic disorder are not completely self-sufficient as adults (Murray and Lopez, 1996), and the course of psychotic illness is often characterized by periodic relapses that persist throughout the life span (Yung and McGorry, 1996). The social and medical costs of psychotic disorders are, therefore, extremely high (Greenblatt et al., 2011; Khaykin et al., 2010; Wu et al., 2005). Schizophrenia continuously ranks among the top 10 causes of disability in developed countries worldwide (Geller et al., 2000; Murray and Lopez, 1996; Wu et al., 2005). On a personal level, the burdens are equally disturbing: patients are typically diagnosed in adolescence or young adulthood and their occupational and social aspirations are derailed (Walker et al., 2008).

In this paper, we provide an overview of the course of psychotic disorders, beginning in the prodromal phase—when subclinical signs first emerge—through the first onset of the clinical syndrome. Because these events almost always unfold between the onset of puberty and the early 20s, this developmental period has come under intense scrutiny by clinical investigators and it is now assumed that a confluence of factors give rise to the onset of psychosis during this period (Walker et al., 2008). We then turn our attention to recent scientific advances in adolescent neuromaturation, as these findings provide a framework for interpreting the rapidly accumulating evidence on neuromaturational abnormalities that precede and accompany the transition to psychosis. Finally, we examine the hormonal and brain changes observed in both psychotic patients and individuals at clinical high risk (CHR) for psychosis. Taken together, the findings suggest that hormonal factors may be involved in neuropathological processes that give rise to the onset of psychosis. This assumption has significant implications for future approaches to preventive intervention.

Background: Current Understanding of the Nature and Course of Psychosis

By contemporary definition, psychotic disorders entail the presence of symptoms which suggest impairment in the individual's understanding of, or contact with, reality (DSM-IV-TR, 2000). The key symptoms of psychosis are referred to as *positive symptoms*, and include delusions, hallucinations, and thought disorder. One or more positive symptoms must be present for a psychotic diagnosis. In addition, psychotic syndromes often include *negative symptoms* which entail deficits in functioning. Among the most common negative symptoms are social withdrawal, anhedonia (reduced emotional experience), and blunted affect (reduced emotional expression). The current psychiatric taxonomy, the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR, 2000) has multiple categories of psychotic diagnoses: schizophrenia, schizoaffective disorder, schizophreniform disorder and mood disorder with psychotic features. It is anticipated that these categories will undergo

revision in the next edition of the DSM (DSM V), now in preparation, largely due to research advances on the origins of psychosis.

Indeed etiologic and diagnostic conceptualizations of psychoses have undergone significant changes over the past two decades. It is now generally accepted that the contemporary DSM diagnostic boundaries distinguishing among psychotic disorders, especially between schizophrenia and other psychotic disorders, do not converge with recent advances in our understanding of genetic and environmental factors that contribute to the diathesis. For example, rapidly accumulating research findings in the field of genetics indicate that many genes contribute incrementally to vulnerability, and these genes are not specific to a single DSM psychotic disorder, but rather confer vulnerability for a range of psychotic illnesses, including schizoaffective disorder and mood disorders with psychotic features (Craddock et al., 2009). Similarly, bio-environmental risk factors, such as prenatal complications (Buka and Fan, 1999) and cannabis use (Moore et al., 2007), appear to be associated with heightened vulnerability for both schizophrenia and the affective psychoses. Given these empirical trends, the term *psychosis* is used in this paper to refer to both schizophrenia and affective psychoses.

The Developmental Course of Psychosis

The ‘diathesis-stress’ model has dominated conceptualizations of psychoses etiology for over four decades (Walker and Diforio, 1997). The basic underlying assumption is that psychotic disorders arise from interaction of pre-existing vulnerability (i.e., “diathesis”) with exposure to various psychosocial and biological stressors that have the potential to trigger its expression.

Vulnerability to psychosis is assumed to originate from genetic factors and fetal brain development abnormalities (Keshavan et al., 2005). Subsequently, adolescent neuromaturational processes are posited to play a role in the clinical expression of psychotic illness, as its clinical onset is typically in late adolescence/early adulthood (Adams et al., 2000; Feinberg, 1982; Keshavan et al., 1994; Keshavan et al., 2005). It has been suggested, for example, that aberrant neural connectivity, acting in concert with dopamine (DA) circuitry abnormalities, arise during adolescence and set the stage for the first psychotic episode (Maccabe, 2008; Walker, 1994; Walker and Bollini, 2002). Psychotic illnesses are, therefore, viewed as neurodevelopmental disorders (Brennan and Walker, 2001).

The Prodromal Stage

The period of functional decline and gradual emergence of attenuated positive symptoms preceding the first psychotic episode can last from a few months to several years, and is referred to as the *psychosis prodrome*. The *prodromal* syndrome usually becomes apparent in adolescence, and is characterized by subclinical manifestations of positive and negative symptoms, as well as nonspecific indicators such as impaired attention, dysphoric mood and declines in role functioning (Ang and Tan, 2004; Fuller et al., 2002; Lencz et al., 2004; Walker et al., 1993; Yung et al., 2004).

Many view the prodromal phase as affording the greatest opportunity for preventive intervention (Addington, 2003; Compton et al., 2007; McGlashan, 2005; Yung and McGorry, 2007), and it has therefore become the focus of more intense research. As a result, several structured approaches to prospectively assess prodromal features have been developed (Correll et al., 2010). These structured interviews yield symptom ratings and utilize standard criteria for designating prodromal status. The term clinical high-risk (CHR) is generally used to refer to individuals manifesting clinical signs that conform to the prodromal criteria used in these measures.

In the US, the *Scale of Prodromal Symptoms* (SOPS) is the most widely used, and, like other prodromal interview schedules, it enhances positive predictive power for designating risk (Miller et al., 2002; Miller et al., 1999). Of those who meet psychosis prodrome criteria, based on the SOPS and similar measures, approximately 20% to 40% develop a psychotic illness within 2 to 4 years (Cannon et al., 2008; McFarlane, 2011; Walker et al., 2010a; Yung et al., 2006). While this level of predictive power is superior to that obtained solely on the basis of having a biological relative with psychosis (Gottesman, 1991; Hans et al., 2004; Kendler and Gardner, 1997), the level of false positives is nonetheless substantial. Thus, by intensifying the focus on CHR individuals who do and do not develop a psychotic disorder, researchers hope to develop measures and algorithms to enhance predictive power. The North American Prodrome Longitudinal Study (NAPLS), for example, is a multi-site project examining a range of biological, behavioral, and clinical factors to enhance prediction, elucidate underlying mechanisms, and identify malleable treatment targets (Addington et al., 2007; Cannon et al., 2008). Hormones are among the biological measures currently under investigation in CHR youth, primarily because of rapidly accumulating evidence of hormonal effects on neuromaturational processes, particularly in adolescence and young adulthood.

Background: Normal Developmental Processes in Hormones and Brain Structure and Function

In recent years, the pervasive role of hormones in modulating neuronal activity and structure has come into clearer focus. Although a comprehensive review is beyond the scope of this article, it is relevant to highlight the emerging trends. Numerous lines of research have elucidated the effects of various hormones on neural activity via binding and modulation of both membrane and intracellular receptors (Guerriero, 2009; Melcangi et al., 2011). Nongenomic mechanisms in hormone activity entail rapid changes via membrane-associated receptors and signaling cascades, whereas slower genomic mechanisms are mediated by nuclear receptors that can regulate gene expression (Falkenstein et al., 2000; McEwen, 1991). Another distinction that has relevance for neuromaturation is that between the activational and organizational effects of hormones (Brown and Spencer, 2012; Sisk and Zehr, 2005). With respect to the brain, organizational effects are conceptualized as those that result in enduring structural changes, while activational effects of hormones entail temporary changes that affect neuronal function. For example, temporary activational effects of adrenal and gonadal hormones on neuronal spine density (Dumitriu et al., 2010; Komatsuzaki et al., 2012; Mendez et al., 2011) and excitability (Groeneweg et al., 2012)

have been demonstrated. Although distinguishing between activational and organizational effects of hormones is complex, especially in research on human brain development, research with animals indicates that both effects play a role in adolescent brain function and development in nonhuman species (Brown and Spencer, 2012).

Peri- and post-pubertal development is associated with dramatic increases in hormone levels and activity, thus advances in our understanding of neurohormonal signaling has implications for our understanding of adolescent brain development. As in the prenatal period, it is now assumed that hormonal changes in adolescence have both activational and organizational effects on the brain (Arnold and Breedlove, 1985; Brown and Spencer, 2012; Charmandari et al., 2003; Peper et al., 2009; Peper et al., 2011a). These effects not only provide a framework for exploring normative adolescent neuromaturation, but also hold promise for shedding light on the mechanisms that contribute to the increased risk for serious mental disorders in the adolescent and young adult stages.

Adolescent Hormonal and Brain Development

Reproductive hormone changes accompanying puberty are well documented. Pubertal onset, marked by reactivation of the hypothalamic-pituitary-gonadal (HPG) axis (Brook, 1999; Dorn et al., 2006), sets the stage for a cascade of hormonal changes that lead to sharp increases in estradiol, progesterone, and testosterone. As illustrated in Figure 1, the hypothalamus releases gonadotropin releasing hormone (GnRH), which triggers an increase in luteinizing hormone (LH) and follicle-stimulating hormone (FSH) from the pituitary gland (Brook, 1999). LH and FSH then stimulate the release of gonadal hormones. Estradiol and testosterone subsequently modulate the release of GnRH and, thereby, the activity of the HPG axis (Dorn and Biro, 2011; Susman and Dorn, 2009).

More recently, research has revealed adolescent developmental changes in the hypothalamic-pituitary-adrenal (HPA) axis. These include a post-pubertal increase in basal and stress-induced cortisol secretion that occurs in conjunction with both age and advancing stages of puberty and appears to extend into the 3rd decade of life in humans (Adam, 2006; Gunnar et al., 2009; Kenny et al., 1966; Lupien et al., 2002; Shirtcliff et al., 2011; Walker et al., 2008; Walker et al., 2001; Walker et al., 2010b). While both males and females manifest an increase in cortisol secretion with age through adolescence, there is some evidence that females show a more pronounced increase (Shirtcliff et al., 2011). A recent review of the literature on pubertal maturation and stress reactivity across species concludes that the pubertal period is associated with an increased biobehavioral reactivity to stress exposure (Foilb et al., 2011; Romeo, 2010). For example, experimental studies of performance and social stress induction indicate that, when compared to children, healthy adolescents manifest a higher baseline and greater cortisol response to both types of stress (Stroud et al., 2009). Thus the HPA axis appears to undergo a maturational increase in baseline activity as well as sensitivity.

Bidirectional influences in HPA and HPG activity during adolescence are apparent, though the specific nature of this relationship is not well understood. As illustrated in Figure 1, it appears that cortisol elevations can inhibit the HPG axis at multiple levels by suppressing

GnRH neurons in the hypothalamus, pituitary release of LH and FSH, and gonadal hormone production (Hiller-Sturmhofel and Bartke, 1998; Kerdelhue et al., 2002; Shi et al., 2011). Increased HPA activation may also play a role in modulating the hormonal cascade that precipitates the onset of puberty. In human females, higher prepubertal cortisol levels are associated with later pubertal growth spurt and menarche onset (Shi et al., 2011). Animal studies suggest that stress exposure can lead to changes in testosterone levels, but only after puberty (Foilib et al., 2011). This suggests that both environmental factors and pubertal stage may influence the relation of HPA and HPG activity. Conversely, the HPG axis is shown to modulate HPA activity. For example, animal studies demonstrate regulatory effects of estrogen on the glucocorticoid and mineralocorticoid receptors, and these effects are moderated by menstrual phase (Carey et al., 1995; Redei et al., 1994). Testosterone also appears to modulate HPA activity, although the mechanisms are not yet clear (Viau, 2002).

Across species, the adolescent period is characterized by changes in brain structure and function, and neuroimaging advances have greatly contributed to our understanding of human brain development (Adams et al., 2000; Blakemore, 2012; De Bellis et al., 2001; Giedd et al., 1999; Giedd et al., 1996; Sowell et al., 2001; Spear, 2000). Adolescent maturational changes are widespread, especially in the limbic structures and the cortex (Giedd et al., 1996; Rapoport et al., 1999; Suzuki et al., 2005), and they entail both regressive and progressive processes (Sowell et al., 2001). Normative adolescent neuromaturation includes reductions in cortical gray matter volume (Giedd et al., 1999), increases in white matter and the volume of some limbic regions (e.g., amygdala, hippocampus) (Peper et al., 2011a), synaptic pruning, and increased myelination and neurogenesis (Giedd, 2004). Further, prefrontal and parietal gray matter volume is inversely correlated with pubertal stage, indicating that pubertal development is associated with processes that entail some regression (Bramen et al., 2011; Peper et al., 2009).

At the functional level, when compared to adult patterns of brain activity, adolescence is characterized by immature executive processing circuits and elevated subcortical activity (e.g., in the striatum) (Luna et al., 2010; Van Leijenhorst et al., 2010). This activational pattern is assumed to shift as development proceeds and neural connectivity changes (i.e., changes in the nature and extent of interconnectivity in neural circuits). Studies using Diffusion Tensor Imaging (DTI) have revealed adolescent increases in white matter integrity and connectivity, as indexed by fractional anisotropy (FA) (Asato et al., 2010). More advanced pubertal development in humans is associated with increased white matter fibers connecting the frontal and temporal regions, as well as between frontal and subcortical regions (Asato et al., 2010). Thus, adolescent white matter maturation is likely associated with enhanced corticocortical connectivity (Asato et al., 2010). Females show earlier and more protracted white matter maturation compared to males, which may be a consequence of the earlier pubertal onset in girls (Asato et al., 2010; Gatzke-Kopp, 2011; Ladouceur et al., 2012). Recent findings from animal studies have also highlighted changes in DA systems during adolescence, with increased connections from DA neurons to the frontal lobes (Spear, 2000). Interestingly, stressful experiences during adolescence have been shown to contribute to sensitivity of the mesolimbic DA system (Gatzke-Kopp, 2011). Further, mesolimbic DA activity is related to psychotic symptoms (Epstein et al., 1999).

Extensive experimental animal research suggests that adrenal and gonadal hormonal changes affect brain organization during adolescence (Cashion et al., 2003; Schulz et al., 2009; Sisk and Zehr, 2005; Vigil et al., 2011; Yates and Juraska, 2008). More recently, studies of human subjects have yielded findings suggesting similar effects. A comprehensive review on the relation of gonadal hormones with brain structure in human adolescents concluded that decreases in prefrontal, parietal, and temporal gray matter were associated with *increased* gonadal hormones (estradiol in girls and testosterone in boys) (Peper et al., 2011a). Thus, rising gonadal hormones may be contributing to some normative ‘regressive’ processes in the cortex. In contrast, increasing gonadal hormones were associated with greater amygdala, thalamus, hippocampal, and parahippocampal volume. In this case, there are ‘progressive’ effects of gonadal hormone increases on subcortical volume. Further, estradiol was positively correlated with gray matter volume in some cortical regions, including the middle frontal gyrus, the inferior temporal gyrus and the middle occipital gyrus (Peper et al., 2011a).

Although there have been relatively few studies of white matter volume and gonadal hormones, a review of the results suggests that testosterone in males and luteinizing hormone in both males and females are linked with puberty-related *increases* in global white matter and regional white matter growth in frontal and temporal connections (Peper et al., 2011a). A study published subsequent to this review used DTI to investigate white matter microstructure in children and young-to-mid adolescents and showed that FA, a measure of white matter integrity, was positively associated with testosterone in boys and estradiol in girls, indicating that rising gonadal hormone levels are facilitating white matter development (Herting et al., 2011).

There is currently only limited research on the relation of cortisol with regional brain volumes in humans, and most of the research has been conducted with clinical populations. Nonetheless, the results are consistent in showing an inverse relation of baseline cortisol with cortical gray matter and hippocampal volume in adults and adolescents (Castro-Fornieles et al., 2009; Mondelli et al., 2010; Tessner et al., 2007). Thus, the increase in cortisol secretion during adolescence may also play a role in brain maturational processes that involve volumetric reductions. The inhibition of neurogenesis may be one mechanism through which glucocorticoids are associated with volumetric reductions. A recent review concluded that elevations in glucocorticoids decrease the rate of neurogenesis in the dentate gyrus of adult rodents (Schoenfeld and Gould, 2012). Relatedly, strategies for reducing or minimizing stressors in adult squirrel monkeys have been shown to facilitate neurogenesis in the hippocampus, presumably through decreasing the levels of circulating cortisol (Lyons et al., 2010).

Research has not yet elucidated the mechanisms mediating the relation between hormones and brain structure in humans, but, as described above, it has been proposed that genomic processes are at least partially involved (Peper et al., 2011b). Thus, hormones may be triggering the expression of genes that influence normal neuromaturational processes, such as gray matter reduction and increased connectivity. Pubertal hormonal changes might also impact both timing and organization of white matter changes, and genetic factors may mediate this process (Ladouceur et al., 2012). It is important to note, however, that the

research on hormone-brain relations in humans presents interpretational challenges, as the processes subserving the relation could reflect either activational or organizational effects of hormones. Further, it is possible that relations between hormone levels and brain characteristics in adolescents are not directly causally linked, but instead are a consequence of other age-related factors that are associated with adolescent development. Nonetheless, the findings highlight the importance of further research aimed at elucidating the mechanisms involved in hormone-brain relations in adolescence. Clearly, elucidating the cascade of hormonal and genetic processes will require longitudinal studies that allow us to characterize individual differences in brain developmental trajectories (Asato et al., 2010).

Hormones and Psychosis

Gonadal Hormones

As noted above, it is assumed that brain maturational processes are playing a role in the expression of the neuropathophysiology subserving psychosis; risk for onset is very low in childhood, then increases with age following puberty and through the third decade of life (Walker et al., 2008). The fact that adolescence/young adulthood is the modal period for the onset of the psychosis prodrome, coupled with the well-established later age at onset of psychotic disorders among females, has generated interest in the relation of gonadal hormone levels with psychosis. It is well established that the timing and pace of pubertal maturation is associated with psychological adjustment (Marceau et al., 2011), and this relation may be mediated by increased exposure or reactivity to stressful events (Ellis et al., 2011; Shi et al., 2011). The research findings to date indicate no association between timing of puberty and risk for psychosis (Golub et al., 2008), however there is evidence that gonadal hormones modulate the expression of psychosis.

Recent comprehensive reviews of the research findings (Hayes et al., 2012; Markham, 2011) concluded the following about estrogen: 1) women with schizophrenia manifest reduced estrogen levels compared to healthy same-sex controls, 2) peak bone mass, an indicator of cumulative estrogen exposure, is significantly lower in women with first episode schizophrenia than in matched controls, 3) in adulthood, risk for psychosis is higher during periods of low estrogen (e.g., during the low estrogen follicular phase of the menstrual cycle and postmenopausal), and 4) adjunctive estradiol may reduce symptom severity in psychotic women. Although the mechanisms involved in the relation of estrogen with psychotic disorders are not understood, it has been suggested that they may reflect anti-dopaminergic and/or neuroprotective effects (Arad and Weiner, 2009). For example, one study showed that estrogen depletion via ovariectomy in rats increased DA D₂ receptor densities in the nucleus accumbens and caudate nucleus, and estrogen treatment reversed the increase and further reduced DA D₂ receptor levels (Chavez et al., 2010). This is consistent with evidence that the behavioral response to antipsychotic drugs, which are DA D₂ antagonists, are decreased following ovariectomy in female rats (Arad and Weiner, 2012) and that estrogen treatment ameliorates psychotic symptoms in humans (Hayes et al., 2012).

Similarly, the review by Markham (2011) concludes that the preponderance of studies find lower testosterone levels in men with schizophrenia, especially those with negative symptoms. Reductions in the free androgen index, a measure of biologically active

testosterone, were recently found in a study of first episode antipsychotic-naïve men with psychosis (Fernandez-Egea et al., 2011). Similarly, lower testosterone levels were reported in a recent study of CHR male adolescents, suggesting that lower levels may precede illness onset (van Rijn et al., 2011).

The origins of the association between gonadal hormone levels and psychosis are not known, and reduced hormone levels could be a consequence of behavioral factors or symptoms. While we are aware of no controlled research on testosterone administration in psychotic patients, as mentioned above, there is accumulating evidence that estrogen administration reduces symptom severity in female patients, and one recent report indicates it may also be beneficial for male patients (Kulkarni et al., 2011).

Adrenal Hormones

Previous reviews have documented heightened cortisol levels in patients with schizophrenia and other psychotic disorders, especially those who are unmedicated (Walker and Diforio, 1997; Walker et al., 2008). These reviews support five general conclusions: 1) indices of HPA activity (cortisol and adrenocorticotropic hormone [ACTH]) are elevated in some patients with schizophrenia and other psychoses, especially in unmedicated and first episode patients; 2) antipsychotic medications typically reduce cortisol, with more pronounced reductions in drug responders; 3) both prescription and recreational drugs that exacerbate or induce psychotic symptoms also increase HPA activity; 4) glucocorticoid receptors appear to be down-regulated in psychotic patients, suggesting reduced negative feedback on the HPA axis, and 5) reduced hippocampal volume, a correlate of hypercortisolemia, is among the most consistently reported brain abnormality in psychotic patients.

Subsequent to these reviews, several other studies have reported heightened cortisol levels in psychotic patients (Guest et al., 2011; Steen et al., 2011; Yildirim et al., 2011). For example, Steen and colleagues (2011) found increased activity of cortisol metabolism in diagnosed schizophrenia patients. Similarly, Guest and colleagues (2011) found elevated cortisol in a large sample of over 200 first- and recent-onset patients. Among patients with mood disorders, those with psychotic symptoms manifest the greatest elevation in cortisol (Stetler and Miller, 2011). Recently, a study of first-episode psychotic patients revealed no differences from control participants in cortisol levels, but the magnitude of the decrease in cortisol over the course of 12 weeks was associated with the decline in severity of psychotic, negative, and mood symptoms (Garner et al., 2011). Further, abnormalities in the HPA axis may be associated with genetic risk for psychosis. Heightened cortisol levels (Yildirim et al., 2011) and more pronounced cortisol reactivity to daily stress (Collip et al., 2011) have been observed in first degree relatives of psychotic patients.

Indices of the biological stress response are of particular interest during the prodromal phase, given that stress is assumed to play a role in triggering symptom expression. To date, only a few published reports have addressed the relation of the HPA system, or its activity, with conversion to psychosis in a CHR or “prodromal” sample. In one study, pituitary volume was measured via magnetic resonance imaging in a CHR group (Garner et al., 2005). The subjects who later developed psychosis ($n = 31$) had a significantly larger baseline pituitary volume compared with those who did not develop psychosis ($n = 63$). The

authors suggested that the larger pituitary volume may be indicative of heightened HPA activation. However, in another report on 23 CHR participants, this same research group found that plasma cortisol showed no significant relationship with global psychopathology, psychotic symptoms, or pituitary and hippocampal volumes (Thompson et al., 2007b). It should be noted that this study had limited statistical power; cortisol was only available for 18 participants in the study, and of these only 5 developed a psychotic disorder. These investigators conducted another study in which they administered the dexamethasone corticotrophin releasing hormone (DEX/CRH) test to twelve CHR individuals (M age = 19.4 years, SD = 3.6; range = 15–25) at baseline; three of the twelve developed psychosis within 2 years (Thompson et al., 2007a). Again, the sample size was small, and given this statistical analyses were not conducted, but the authors reported that, contrary to findings on studies of psychotic patients (Walker et al., 2008), participants who *did not* develop psychosis nevertheless showed a trend toward higher plasma cortisol levels at the latter stages of the test, when compared to the three participants who did develop psychosis.

In contrast, studies of larger samples demonstrate that CHR participants who develop psychosis do manifest higher cortisol levels compared to those who do not (Walker et al., 2001; Weinstein et al., 1999). For example, a recent study of 56 CHR youth (age: 12 to 18) found that those who go on to develop a psychotic disorder showed significantly higher cortisol levels (Walker et al., 2010a). Thus, when compared to the CHR subjects who did not develop a psychotic disorder within the 4-year follow-up period, the 14 later diagnosed with psychosis manifested higher cortisol levels over the first year following baseline. This study had the advantage of multiple saliva samples over a period of one year to enhance cortisol estimation reliability. As in previous studies of adolescent HPA activity, an age-related increase in cortisol secretion was observed in both the healthy and CHR groups, consistent with the evidence reviewed above that the developmental period of heightened risk for prodromal symptom onset may also be characterized by greater stress sensitivity (Stroud et al., 2009). Using similar methods, a recent investigation of baseline cortisol levels from the ongoing NAPLS project reported significantly higher salivary cortisol levels in CHR subjects ($n = 260$) than healthy controls matched on age and sex (Walker et al., *submitted*). Cortisol levels were also positively—though modestly—correlated with ratings of positive, negative, disorganized, and general prodromal symptoms.

The above findings raise important questions about the significance of elevated cortisol in individuals at risk for psychosis. A recent review of the extensive literature on stress and psychosis concludes that, when compared to controls, psychotic patients and pre-psychotic CHR individuals do not report significantly increased numbers of stressful life events, but they do report more subjective distress in response to stressors (Holtzman et al., 2013). Thus elevated cortisol levels in psychotic and CHR groups may reflect a greater sensitivity to stress, rather than greater stress exposure. Further, there is evidence of a causal relation between cortisol and psychosis: both administration of steroids and Cushing's disease, which involves heightened cortisol, are associated with increased risk of psychotic disorders (Ross and Cetas, 2012). Also noteworthy, case studies of Cushing's patients indicate that psychotic symptoms remit after treatment is successful in reducing cortisol levels (Chana et al., 2011).

In summary, there is evidence of reduced HPG activity, but increased HPA activity in psychosis (Davidson and Heinrichs, 2003; Hill et al., 2004). The origins of these abnormalities and the interactions between these two axes remain unclear. Nevertheless, the importance of this area of investigation has been highlighted by advances in our understanding of neurohormonal signaling, epigenetic processes, and brain abnormalities in the etiology of mental disorders. Rapidly increasing evidence suggests that abnormalities in brain maturation characterize CHR individuals, and elucidating the pathways that affect these neuromaturational abnormalities is a high priority.

Brain Development and Psychosis

A large body of research has documented a range of abnormalities in brain structure in psychoses. These include decreased volumes in the hippocampus (Adriano et al., 2012) and superior temporal gyrus (Siever and Davis, 2004), decreased frontal functioning (Davidson and Heinrichs, 2003; Hill et al., 2004), and increased pituitary volume (Garner et al., 2005; Mondelli et al., 2008; Pariante et al., 2005; Pariante et al., 2004; Takahashi et al., 2009). Recent systematic reviews on volumetric differences between psychotic patients and healthy controls conclude that there is a generalized reduction in cortical gray matter volume in most regions, and this characterizes both first episode and chronic patients (Arnone et al., 2009; Levitt et al., 2010). These abnormalities appear to increase over the course of illness, in at least some patients (Hulshoff Pol and Kahn, 2008). Further, studies of patients with psychosis onset during adolescence indicate that the gray matter volumetric reductions, relative to sameage healthy controls, are more pronounced the earlier the onset of the illness (Douaud et al., 2009). Finally, comparisons of monozygotic twins discordant for schizophrenia indicate that the volumetric reductions are more pronounced in the affected co-twin, especially for the perihippocampal region, indicating that the brain abnormalities in psychotic patients are partially independent of genetic factors (Borgwardt et al., 2010; van Haren et al., 2004).

More recently, volumetric abnormalities have been documented in CHR individuals, with more significant volumetric reductions in those who develop psychosis (Fusar-Poli et al., 2011; Puri, 2010; Smieskova et al., 2010). Consistent with evidence of heightened HPA activity preceding and following the onset of psychoses, the hippocampus appears to be a brain region with marked volumetric reduction in patients with psychotic disorders, as well as in those at elevated risk for psychosis (Witthaus et al., 2009). For example, a meta-analysis of data from over 700 healthy control and 800 CHR subjects revealed reduced gray matter volume in the parahippocampal/hippocampal regions, anterior cingulate, right superior temporal gyrus, left precuneus, left medial frontal gyrus, and right middle frontal gyrus for the CHR group (Fusar-Poli et al., 2011). Among the CHR participants, those who later developed psychosis showed lower baseline gray matter volume in the right inferior frontal gyrus and in the right superior temporal gyrus (Fusar-Poli et al., 2011).

In light of the normative decrease in gray matter volume associated with adolescent and young adult development, the more pronounced gray matter declines in CHR individuals have led some to propose that risk for psychosis involves an abnormal acceleration in the brain developmental processes associated with adolescence (Fusar-Poli et al., 2011; Walker

et al., 2008). Thus, brain organizational processes may go awry and disrupt neural circuitry (Whitford et al., 2011). Further, it has been suggested that this aberrant process, as well as the brain abnormalities associated with psychosis, may partially reflect the adverse effects of persistent glucocorticoid elevations on brain structure (Walker et al., 2008).

Neurodevelopmental Models of Schizophrenia and Other Psychoses

Given evidence that the prodrome to psychosis is associated with increased activity of the HPA axis and, potentially, decreased HPG activity, the role of hormones in the expression of psychosis is becoming more salient. The scientific community has long recognized the relation between the onset of puberty and risk rates for many forms of psychopathology (Adams et al., 2000; Graber et al., 1997), and recent developmental models of psychosis posit that hormones modulate the expression of vulnerability to psychiatric disorders (van Wingen et al., 2011; Walker et al., 2008). Further, because DA, more than any other neurotransmitter, has played a prominent role in the neurobiological theories of psychosis (Carlsson, 1988; Meltzer and Stahl, 1976; Winterer, 2006), it has been featured heavily in neurodevelopmental models (Murray et al., 2002; Tan, 2009; Walker and Diforio, 1997). The preponderance of evidence suggests that heightened DA activity is associated with both psychosis and psychosis risk. Maturation increases in DA activity during adolescence have thus been cited to account for the modal age at onset of schizophrenia and other psychoses (Benes, 2003; Walker, 1994; Walker and Bollini, 2002).

Aberrant functional connectivity, acting in concert with increased activity in DA circuitry during adolescence, may be the final common pathway setting the stage for the onset of psychosis (Maccabe, 2008; Walker, 1994; Walker and Bollini, 2002). Of course, neurotransmitter systems interact, and glutamate, GABA, and serotonin have also been implicated in etiology, in part due to their effects on the DA system (Howes and Kapur, 2009).

Stress has been a central feature in many theories of the neurodevelopment of schizophrenia, and research evidence supporting a role for HPA hyperactivity in psychosis is substantial (Holtzman et al., 2013). The adverse effects of persistent glucocorticoid elevations on brain structure/function are also well documented (Arnsten, 2009; Frodl and O'Keane, 2012), thus recent models of psychosis etiology have hypothesized that cortisol elevations in CHR individuals may be contributing to brain structural abnormalities that precede psychosis. Such effects may be organizational, in that they permanently compromise brain structure. Of course, the results of research on Cushing's patients, as described above, suggests that there are also adverse activational effects of elevated cortisol that can be reversed.

As noted above, with respect to the HPG axis, theorists have speculated on how estrogen might influence the expression of psychosis by suppressing DA activity, thereby dampening its adverse effects, delaying psychosis onset, and improving prognosis in women (Riecher-Rossler and Kulkarni, 2011). Coupled with the evidence that symptom severity changes in conjunction with estrogen levels during the menstrual cycle, and that estrogen administration reduces symptom severity in both sexes, these findings suggest activational effects of estrogen that modulate the neuropathophysiology underlying psychosis.

The complex interactions between the HPG and HPA axes should also be considered with regard to the emergence of psychosis. There is extensive evidence that stress exposure and glucocorticoids affect HPG activity (Hiller-Sturmhofel and Bartke, 1998; Kerdelhue et al., 2002; Shi et al., 2011; Viau, 2002). In fact, it is well established that glucocorticoid secretion exerts inhibitory effects on reproduction and acts at multiple levels of the HPG axis. Specifically, as illustrated in Figure 1, glucocorticoids can suppress GnRH neurons, the pituitary gonadotropin secretion, and production of gonadal hormones. It is possible that reduced gonadal hormone levels observed in psychotic patients and CHR individuals reflect the suppression of HPG function by elevated glucocorticoid secretion.

Research findings on the effects of HPG activity on HPA function in humans are more limited, although some findings suggest that estrogens may suppress glucocorticoid secretion (Patacchioli et al., 2006). If this is the case, then glucocorticoid-induced reductions in HPG activity may, in turn, further contribute to glucocorticoid elevations. The cumulative effects could be a disruption in adolescent neuromaturational processes that appear to be exaggerated in psychosis; namely, the more pronounced developmental increase in cortisol secretion (Walker et al., 2010a), decrease in gray matter volume (Sowell et al., 1999), and pruning of synapses (McGlashan and Hoffman, 2000).

Summary and Conclusions

As our scientific understanding of adolescent brain development and neurohormonal mechanisms has grown, the range of processes that have the potential to derail neuromaturation and give rise to psychosis have become more apparent. As described above, steroid hormones may contribute to the pathogenesis of psychosis at the genomic level, disrupting brain development by triggering the expression of latent vulnerability genes or by altering the expression of genes that govern normal brain development (Walker and Bollini, 2002). At this point, our understanding of hormonal and brain changes in the prodromal phase of psychosis is too limited to posit specific genes or neural mechanisms. Future examinations of the interaction of adrenal and gonadal hormones and their relationship with aberrant brain development in the psychosis prodrome are the next steps for delineating these mechanisms.

Along with advances in our understanding of the etiology of psychosis, the possibilities for preventive intervention are coming into clearer view. If it is the case that the adolescent hormonal milieu is playing a role in the pathogenesis of psychosis, then prevention may involve modulations aimed at normalizing or constraining aberrant hormonal processes. Furthermore, there is reason to believe that identification of specific neurohormonal triggers during adolescence could possibly hasten treatment onset, thereby increasing positive outcomes in individuals at greatest risk for psychosis (Drake et al., 2000; Johannessen et al., 2001; McGlashan et al., 2001).

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Highlights

- An overview of the nature and course of psychosis during adolescence is provided.
- We review the potential role of hormones in abnormal brain changes in adolescence.
- We discuss hormones in relation to neuropathological processes in psychosis onset.

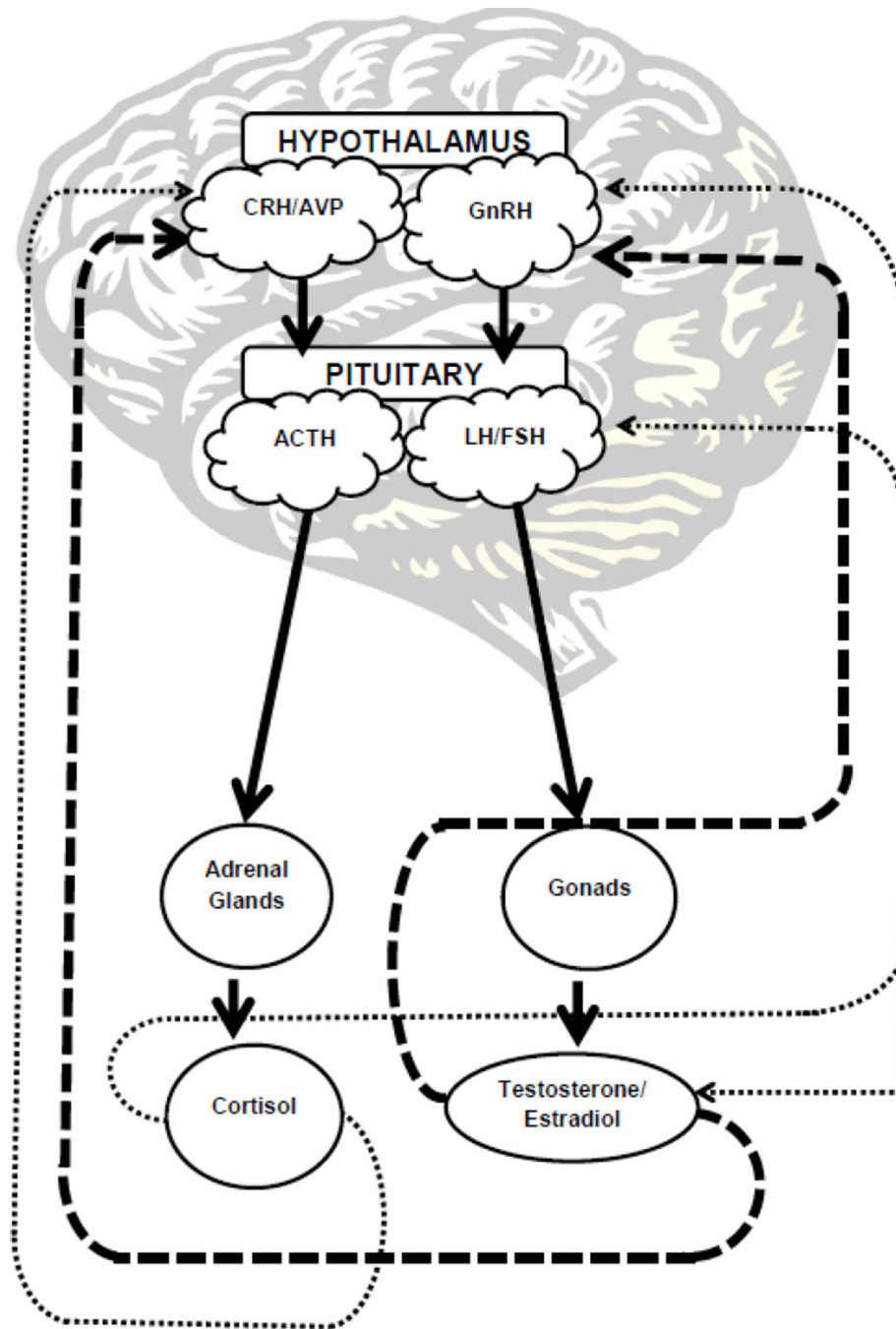


Figure 1. The Brain Regions and Chemical Messengers involved in the HPA and HPG axes
 The dashed lines indicate inhibitory pathways and the solid lines represent activational pathways. In the psychosis prodrome, the increase in HPA activity may be suppressing the HPG axis, and contributing to abnormalities in the balance and progression of hormonal changes that influence normal adolescent brain changes.