SEX DIFFERENCES IN ADOLESCENT DEPRESSION

Bachelor Degree Project in Cognitive Neuroscience
Basic level 22.5 ECTS
Spring term 2018

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Abstract
At the age of 13, the 2:1 ratio becomes evident. It entails the fact that after puberty, twice as many females as compared to males suffer from depressive episodes. Much research has been conducted to highlight key contributing factors that aid in the onset and the timing of the 2:1 ratio. Many researchers emphasize hormonal influences and the onset of puberty as key contributors, with theories such as the gonadic theory and the interactional hypothesis both highlighting the role of hormones in the existence and the emergence of the 2:1 ratio during adolescence. Furthermore, a large variety of researchers emphasize females increased stress sensitivity and stress reactivity as key contributors to the 2:1 ratio. Critically, research concerning hormonal- and stress-related factors will be included. However, an additional focus will be on neurodevelopmental sex differences. This, as brain-based sex differences have been paid too little attention in theories and models concerning the emergence of the 2:1 ratio during adolescence. Results from research conducted to unravel the mystery of sex differences within the adolescent brain emphasize the impact of sex hormones on the maturational sexual differentiation occurring within the adolescent brain. It has been hypothesized that increases in female adolescent depression might occur in accordance with upsurges in peripheral estrogen levels, during puberty. This seems to suggest that there is an interaction between the effects of circulating ovarian hormones in relation to both sexual differentiation in brain organization and depression susceptibility. Hence, the point of this essay is to delineate key contributing factors that potentially govern the existence and onset of the 2:1 ratio during adolescence by emphasizing the areas of (a) sex-based neurodevelopmental factors, (b) hormonal factors and (c) stress-related factors.

Keywords: sex differences, adolescent depression, female adolescent depression, neurodevelopmental changes, sex differences in brain maturation, 2:1 ratio.
1. Introduction

For many adolescents, their lives are characterized by storm and stress. After puberty, the occurrence of depression increase markedly and most individuals who are deemed to suffer from a mental disorder start to display adjustment problems (Walker, 2002). Moreover, a rapidly growing body of research highlight that puberty marks the entrance into a sensitive developmental period and that psychiatric disorders such as depression and anxiety, often has its onset during the adolescent years (Emslie, Mayes, & Ruberu, 2006; Forbes & Dahl, 2012; Patton et al., 1996; Walker, 2002). Furthermore, at the ages of 13 years (Salk, Petersen, Abramson, & Hyde, 2016), 13-15 years (Essau, Lewinsohn, Seeley, & Sasagawa, 2010) 13-18 years (Andersen & Teicher, 2008), 13-19 years (Faravelli, Scarpato, Castellini, & Sauro, 2013) the 2:1 ratio become evident, which refers to the fact that twice as many females as compared to males are depressed after puberty (Aube, Fichman, Saltaris, & Koestner, 2000). The emergence of the 2:1 ratio after puberty has gained consistent support (Bennetta, Ambrosini, Kudes, Metz, & Rabinovich, 2005; Buwalda, Geerdink, Vidal, & Koolhaas, 2011; Weiss, Longhurst, & Mature, 1999) and is considered to be one of the two most replicated findings in psychology (Silberg et al., 1999; Weiss et al., 1999). The second most replicated finding in psychology is the causal relationship between stressful life events and depression (Kendler, Thornton, & Prescott, 2001).

Adolescence is considered the transitional period between childhood and adulthood. It begins with the naturally occurring physiological condition of puberty and ends when the individual takes on adult social roles and responsibilities (Forbes & Dahl, 2012; Sturman & Moghaddam, 2011). Puberty itself involves increased growth, changes in body composition, the development of gonads and secondary sexual organs, cardiovascular and respiratory changes. Puberty typically has its onset at the age of 10-17 in girls and 12-18 in boys.
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(Sturman & Moghaddam, 2011). Puberty will be included more in-depth further on in addition to its potential role in the emergence of the 2:1 ratio. However, the transitional period of adolescence contains not only puberty but is also highlighted by the vast variety of cognitive, behavioral and psychological changes (Blakemore, 2007; Giedd et al., 2006; Walker, 2002). However, the various changes do not all start and end together, thus relating adolescent brain changes with behavioral changes is extremely challenging and should be done with the utmost care. Understanding the vast array of neurobiological changes that drive everything from the fountain of hormonal signals that initiate puberty, to the increased cognitive abilities and motivational changes is crucial for understanding the difference between normal behavioral tendencies present in adolescents from the pathological conditions they are also so vulnerable to (Sturman & Moghaddam, 2011).

Moreover, much research has been conducted on the emergence of the 2:1 ratio after puberty. As a result, many different factors have been attributed to playing a key role in its onset. A variety of researchers (Andersen & Teicher, 2008; Angold, Costello, & Worthman, 1998; Goodyer, Herbert, Tamplin, & Altham, 2000; Halbreich & Kahn, 2001; Hankin, 2015; Hyde, Mezulis, & Abramson, 2008; Naninck, Lucassen, & Bakker, 2011; Patton et al., 1996; Steiner, Dunn, & Born, 2003; Walker, 2002) have emphasized the role of biological factors on depressive symptoms. According to Patton et al. (1996), the cyclical gonadal hormone secretion may trigger mood disorders in women. The impact of hormones is also emphasized by a longitudinal study conducted by Salk et al. (2016) and the results emphasize different developmental trajectories between the sexes in the depressive onset. Moreover, the girls’ rate of a depressive diagnosis increased between the ages of 11-14 years, as compared to the boys’ depressive rates that increased from 15-18 years. Furthermore, at the age of 20 years, 24% of adolescent females had experienced depressive symptoms and 15% of adolescent males (Salk
et al., 2016). However, according to Whittle et al. (2014), 14% of males and 28% of females had experienced a depressive episode by the age of 18 years. Several researchers have suggested that a potential shift occurs around the age of 13 years (Cyranowski, Frank, Young, & Shear, 2000; Essau et al., 2010), before the age of 13 more boys than girls show depressive symptoms and after age 13, the 2:1 ratio becomes evident. Furthermore, before the age of 13 boys also reported more negative life events and again after 13 years girls instead reported more negative life events. Results, like those mentioned above, support the gender-linked difference in the stress-depression relationship (Cyranowski et al., 2000). Additional, support for sex differences in the stress-depression relationship will be included further on in the context of parental depression (Kessler, Avenevoli, & Merikangas, 2001), aversive childhood experiences (ACEs; Chapman et al., 2004), sex hormones (Oldehinkel & Bouma, 2011) and sex differences in sensitivity to abnormal brain development within the hippocampus (Whittle et al., 2014).

Critically, the point of this essay was not to present a critical review of all the available literature or to include all the possible variables that may contribute to the existence or onset of the 2:1 ratio. Due to space limitations, an admittedly selective viewpoint of factors will be highlighted. Moreover, there are numerous contributing factors that have been emphasized to aid to the emergence of the 2:1 ratio during adolescence, that due to lack of range have not been included in the essay. Some of these contributing factors will briefly be presented below. First, a main contributing factor to the 2:1 ratio and depression, is emphasized to be genetics. Furthermore, according to a study conducted with adolescent female twins \(N = 3316\) by Glowinski, Madden, Bucholz, Lynskey, and Heath, (2003) genetic factors were calculated to account for about 44.4% of the underlying variance behind major depression. Moreover, the role of genetics have been highlighted by several researchers
Adolescence is a period that encompasses substantial dopaminergic system development and there are notable sex differences evident, thus dopamine may also play a role in the emergence of the 2:1 ratio and sex differences in motivated behavior during adolescence (Andersen, Thompson, Krenzel, & Teicher, 2002; Casey, Jones, & Hare, 2008; Davey, Yücel, & Allen, 2008; Forbes & Dahl, 2012; Sturman & Moghaddam, 2011). Moreover, other factors that have been emphasized to contribute to the emergence of the 2:1 ratio are: females greater tendency towards ruminative coping (Nolen-Hoeksema & Girgs, 1994), females increased dependence of relationships and affective needs (Cyranowski et al., 2000), greater cognitive vulnerability (Hankin & Abramson, 2001), gender roles (Aube et al., 2000). However, all these factors undeniably all play a role in the development of adolescent depression (Hyde et al., 2008), in addition to many other factors not included here.

The aim of this essay is to clarify key contributing factors that potentially aid the emergence of the 2:1 ratio during adolescence. Neurodevelopmental changes that may contribute to the onset of the 2:1 ratio will be particularly emphasized. The areas included in this essay, have been chosen due to their dynamic interplay in addition to their central role in theories and models concerning the emergence of the 2:1 ratio. The focus will be on 3 main areas: (a) brain maturation and sex difference evident within the brain during adolescence, (b) pubertal onset and upsurges in sex hormone in addition to their potential interaction with the brain, genetics, and stress, (c) stress and different stressors such as aversive childhood experiences (ACEs) and parental depression will be included. Followed by theories and
models concerning adolescent depression and the onset of the 2:1 ratio. To conclude, a discussion and a conclusion will be encompassed. Yet, it must be noted that no simple answer is expected to be given, as this is an extremely complex area and many contributing factors are relevant and as noted and not all can be included in this essay. However, to clarify what potentially establishes the 2:1 ratio and its emergence during the transitional period are crucial so that relevant knowledge about the 2:1 ratio can become more widespread to the general population. Additionally, to aid the progress of advanced interventions and strategies to prevent and treat the different subtypes of depression apparent amongst the sexes. An important limitation is to be noted, the essay will only focus on the adolescent period. Thus, factors that contribute to the 2:1 ratio during adulthood is not included.

2. Adolescent Depression

A serious and common disorder in adolescence is major depression (Andersen & Teicher, 2008; Blom et al., 2016; Casey et al., 2008; Oldehinkel & Bouma, 2011; Patton et al., 1996; Walker, 2002). The lifetime prevalence of the disorder increases dramatically from 1% of the population under the age of 12 years to 17-25% of the population by the end of puberty (Glowinski et al., 2003; Kessler et al., 2001). Depressive disorders as such can be more or less severe (Emslie et al., 2006; Gazzaniga, Heatherton, & Halpern, 2013; Miller, 2007). For an individual to be diagnosed with MDD according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5; American Psychiatric Association [APA], 2013) 5 or more of the following symptoms must be present during the same 2 week period and evident most days: depressed mood, diminished interest in all pleasure, appetite and weight changes, insomnia or hypersomnia, retardation, loss of energy, concentration difficulties, feelings of self-reproach, excessive and inappropriate feelings of guilt and frequent thoughts of death or even perhaps suicide (APA, 2013).
Furthermore, MDD varies in severity and those individuals who become diagnosed with the condition, suffer from severe impairments which tends to persist for at least 2 weeks to several months and sometimes even lasting for years. Contrary to major depression, dysthymia is mild to moderate in severity but lasts a minimum of 2 years. The same symptoms are often evident but not severe enough to be diagnosed with MDD (Morrison, 2014). Critically, the distinction between a depressive personality, dysthymic disorder and MDD is somewhat unclear. A dimensional view is helpful when considering the mentioned disorders as they do not appear distinct but rather points along a continuum (Gazzaniga et al., 2013). Note, this is a general definition of depression, thus it was not proposed with adolescent depression in mind.

The symptoms evident during an adolescent's depressive episode is comparable to the symptoms evident during an adult depressive episode (Andersen & Teicher, 2008; Emslie et al., 2006; Naninck et al., 2011), yet, adolescents are suggested to display more irritability rather than sadness which is more pronounced in adult depression (APA, 2013). In addition, adolescent depression shows higher comorbidity with anxiety, conduct problems, and learning disability rather than substance abuse and sociopathy which are more pronounced in adult depression (Andersen & Teicher, 2008; Emslie et al., 2006; Naninck et al., 2011). What's more, depression that strikes during the adolescent years has a 40% chance of the individual experiencing recurrent episodes later in life. Adolescent females are suggested to have a higher risk of experiencing recurrent episodes according to Naninck et al. (2011). However, Kessler et al. (2001) do not agree with this notion and instead suggest equal recurrence rates, recovery time and speed of episodes. Nonetheless, if left untreated, adolescent depression can
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Persist into adulthood and significantly increases the risk of developing other psychopathologies (Naninck et al., 2011).

Furthermore, a study by Zisook et al. (2006) emphasize adolescent MDD to be more chronic, severe and a more disabling form of MD then that which has its onset later in life. Moreover, according to Andersen and Teicher, (2008) depressed adolescents display more anhedonia, hypersomnia, decreased ability to think and concentrate, melancholia as well as suicidal tendencies than that of depressed children. Furthermore, a greater disturbance in circadian rest-activity rhythms is also apparent (Andersen & Teicher, 2008). Critically, the most severe negative outcomes of adolescent depression are suicide attempts, substance abuse (which is also evident in adolescence depression but is more pronounced in adult depression), academic decline, employment incapacity and finally suicide (Emslie et al., 2006; Miller, 2007). Furthermore, according to Zisook et al. (2006), higher rates of suicide attempts are evident during an adolescent onset of MDD, as compared to when MDD first emerges in adulthood (Zisook et al., 2006). Conversely, the incidences of suicide unfold with age, before the age of 10 it is rare, but increases 100-fold between the ages of 10 to 14 and rises an additional 10 times between the ages 15 to 19 years (Andersen & Teicher, 2008). According to Naninck et al. (2011) as many as one-third of all adolescents suffering from depression attempt suicide and between 4-10% of them succeed, making depression a major cause of death among adolescents.

2.1 Sex Differences in Adolescent Depression

A multitude of studies, conducted in different countries, highlight that twice as many women are depressed as men and that this sex difference first appears during adolescence (Andersen et al., 2002; Angold et al., 1998; Bouma, Ormel, Verhulst, & Oldehinkel, 2008;
Buwalda et al., 2011; Glowinski et al., 2003; Weiss et al., 1999). Critically, part of the pronounced sex difference evident may be due to a notable difference in help-seeking behavior and symptoms reporting among the sexes. Females are more likely to seek treatment for psychological problems earlier, where males are more prone towards alcohol and drug abuse to cope with depressive symptoms. Nonetheless, it is unlikely that the differences in help-seeking behavior account for the preponderance of the sex difference evident in depression as this difference has been highlighted in both clinical studies as well as nonclinical populations (Naninck et al., 2011). More females as compared to males attempt to commit suicide, however, more males are successful in their suicide attempt. The cause behind the sex-difference in suicide success has been hypothesized to be due to males increased aggressiveness also towards themselves, whereas females are more prone to self-harm behaviors (Värnik, 2012).

Conversely, boys display more depressive symptoms than girls prior to mid-puberty which is then reversed and the opposite occurs after puberty (Angold et al., 1998; Glowinski et al., 2003; Kessler et al., 2001; Wade, Cairney, & Pevalin, 2002). Thus, the increase in adolescent female depression may be linked (although temporarily) to the onset of menarche, suggesting underlying hormonal mechanisms (Patton et al., 1996). Hence, it has been suggested that the pubertal stage of the individual is a better predictor than age in terms of depressive symptoms (Kessler et al., 2001; Oldehinkel & Bouma, 2011; Patton et al., 1996). Pubertal changes are often referred to by five Tanner stages, stage one referring to infertility and stage five to a completed pubertal process (Oldehinkel & Bouma, 2011). It is within the third stage (mid-puberty) that the increased risk of depression becomes evident (Angold et al., 1998), the third stage is also correlated with changes in androgen and estrogen levels.
Temporarily making pubertal development a stronger predictor of depression than age (Angold et al., 1998; Oldehinkel & Bouma, 2011; Patton et al., 1996).

In line with this, a study by Angold et al. (1998) found increased mental health problems in term of social uncertainty, depressed mood and increased worries with the continued development of each Tanner stage in girls, however, this was not noted in boys (Angold et al., 1998). Evidence suggests that the increased risk of depression may be a result of increased sensitivity to stressful life events and particularly increased interpersonal stressors, which are more evident in the life of adolescent girls (Aube et al., 2000). This in addition to genetic risk factors and stress sensitivity being expressed differently in girls, is highlighted as important contributing factors to the noted sex difference (Oldehinkel & Bouma, 2011). Furthermore, girls are also affected differently by environmental adversity than boys, these sex-related differences have also been reported in an increased hypothalamic-pituitary-adrenal cortex (HPA) axis response to both internal and external influences, suggesting a potentially increased malleability of adolescent girls (Oldehinkel & Bouma, 2011). The HPA-axis is one of the body's major stress systems and will be described in more depth further on.

Furthermore, a study conducted by Bennetta et al. (2005) highlights that girls experienced more feelings of guilt and body dissatisfaction and displayed higher rates of feelings of sadness/depressed mood, self-disappointment, self-blame, feelings of failure, concentration problems and work difficulties, fatigue and health worries. Concentration problems are highlighted to be an important difference between the sexes and may be a result of girls also displaying more rumination, which is also linked to depression. Boys, on the other hand, had higher clinical ratings of anhedonia, depressed morning mood, and morning
fatigue but also emphasize more feelings of boredom which may explain the increased anhedonia evident among boys (Bennetta et al., 2005). The emergence of guilt may be an important contributing factor for the development of depression in girls, as girls often are thought to be more sensitive and protective of their surroundings rendering them more sensitive to feelings of guilt. Increased gonadal hormones underlie morphological changes evident in early adolescence, these bodily changes in addition to the shift in social interactions (as the social milieu become increasingly complex) may increase the importance of peer evaluation and also self-consciousness. Critically, girls tend to evaluate the bodily changes associated with puberty, such as weight increase and body shape transition, negatively and might, therefore, be more troubled by these changes than their opposite sex (Bennetta et al., 2005). Body dissatisfaction is prevalent among many depressed girls, both current and previously conducted research has found a mediating link between body dissatisfaction and depression in girls. Noteworthy, restrained eaters which are more common among girls tend to eat more when stressed and restrained eating has also been linked to depressive symptoms. Thus, stress may generate overeating leading to increased body dissatisfaction and potentially depressive symptoms (Bennetta et al., 2005).

3. The Adolescent Brain

Adolescence encompasses dramatic structural and functional neurodevelopment. Adolescence also encompasses rapid cortical maturation (increased synaptic pruning, myelination and synaptic plasticity) of neural areas involved in emotional perception, regulation and reward processing (Kerestes, Davey, Stephanou, Whittle, & Harrison, 2014). In addition to neurobiological changes that drive everything from the fountain of hormonal signals that initiate puberty, to increased cognitive ability and motivation changes (Sturman & Moghaddam, 2011). Hence, much is happening within the brain during adolescence,
undeniably some of these alterations contribute to the onset of adolescent depression and the emergence of the 2:1 ratio. The following section will provide neurodevelopmental research concerning the adolescent brain, specifically relating to adolescent depression and the sex difference evident.

3.1 Adolescent Depression and the Brain

Before all else, key neurodevelopmental processes will be introduced to emphasize the vast array of ongoing alterations occurring within the maturing adolescent brain. This to highlight their crucial role in transforming the adolescent brain into an adult. Conversely, in the early stage of development, the brain begins to form new synapses, resulting in a synaptic density far exceeding that of adults. The process of synaptogenesis can take several months. Consequently, a one-year-old baby's brain accommodates many more connections than that of an adult brain. However, the following stage in development is the reduction of unused synapses to an adult number, this process of synaptic elimination is often referred to as synaptic pruning. The pruning of excessive synaptic connections is similar to that of pruning a rose bush, weak branches are removed to allow remaining branches to grow stronger (Casey, Tottenham, Liston, & Durston, 2005). Thus the infrequently used connections are eliminated and frequently used connections strengthened. This experience-dependent process reduces the overall synaptic density to that of adult levels ordinarily by the time of sexual maturity, the process is believed to be responsible for adequately fine-tuning the network of the brain (Blakemore, 2007; Casey et al., 2005).

Other important developmental mechanisms are myelination, often referred to as white matter (WM). Myelin function as a fatty substance that insulates the axon of the neuron as it continues to develop, the myelin tremendously increase the speed of the electrical
impulses from one neuron to the other. Sensory and motor brain areas become myelinated during the first few years of life but axons in the frontal cortex continue to be myelinated well into adolescence. As a result, the frontal cortex neuronal transmission speed is believed to increase after puberty (Blakemore, 2007). The synaptic pruning and myelination occurring specifically in the prefrontal cortex, are two processes that contribute to the continued refinement of cognitive abilities assumed to occur during the transitional period. They are also often included in theories concerning the development of mood disorder and will be discussed more in depth further on (Davey et al., 2008). Furthermore, the next section will be on the brain structure consisting of the hippocampus, the PFC, and the amygdala, as they play a key role in the etiology of adolescent depression (Andersen & Teicher, 2008; Naninck et al., 2011; Russell & McEwen, 2006). These brain structures also regulate the HPA-axis, which in turn is crucial for controlling the neuroendocrine feedback of stress hormones (Naninck et al., 2011).

The hippocampus continues to develop well into the period of adolescence (Russell & McEwen, 2006). Moreover, the hippocampus is critical for memory, spatial and emotional learning but does most likely also have an important part to play in adolescent depression (Naninck et al., 2011). This as the hippocampus plays a central role in the regulation of mood as well as its hypothesized response to antidepressants (Andersen & Teicher, 2008). In addition to its vital role in regulating the HPA-axis, which in turn plays a crucial role in controlling the neuroendocrine feedback of stress hormones (Naninck et al., 2011). What's more, half of all depressed patient is emphasized to show evidence of a hyperactive HPA-axis. Furthermore, the hippocampus shows clear stress susceptibility (Naninck et al., 2011). This has been suggested due to the notion of a reduced hippocampal size is often evident in depressed adults, however, the effects vary due to duration and recurrence of the episodes (Videbech & Ravnkilde, 2015).
The hippocampus role in depression has also been suggested to be failing to provide accurate and varied contextual response to emotionally laddered stimulation. This is emphasized by findings concerning fearful faces in children and adolescents with MDD (Pine et al., 2004). Critically, few studies have investigated the hippocampal size of adolescents and depression, also the existing results are uneven and yield more questions than answers (Andersen & Teicher, 2008). Furthermore, a significant left and right reduction in hippocampal volume, with increased left side were noted in a study conducted by MacMaster and Kusumakar, (2004) in a sample of older adolescents, (mean age 14 years, \( n = 23 \) versus controls \( n = 23 \)). However, it must be noted that the study may have been confounded by comorbid anxiety. An area also showing uneven results is reduced hippocampal volume due to early maltreatment. Five studies (total \( n = 209 \)) have highlighted reduced hippocampal volume in adults exposed to childhood abuse, while three other studies (total \( n = 186 \)) did not find such result in children within an equal family history of abuse. However, the difference may be due to the effects of the abuse not showing yet, thus it is only in adulthood that the reduced hippocampal volume can be expected (Andersen & Teicher, 2008). However, according to Naninck et al., (2011) a 10% reduction in hippocampal volume is often found in depressive patients.

Furthermore, Russell and McEwen, (2006) suggest that the effects of chronic stress on the developing adolescent hippocampus may be delayed and are not revealed until the stressor has been terminated. Russell and McEwen, (2006) also suggest that the adolescent hippocampus just as adults are sensitive to stress. However, the effects are not revisable as seen in adults but result in long-lasting and potentially permanent damage. When looking to animal studies on the effects of stress on the hippocampus, evidence suggests that the reduced
hippocampal volume emerges during puberty and early adulthood, where a reduction of 34-36% is evident in synaptic density (Andersen & Teicher, 2004). Thus, the noted research suggests that adversity occurring within a window of vulnerability set in motion processes regulating synaptic overproduction (Andersen & Teicher, 2008).

Another brain area involved in depression is the PFC, maturation of the PFC is suggested to lead to continued refinement of abilities as cognitive control, the regulation of emotional behaviors and fear extinction (Russell & McEwen, 2006). Multiple components of the PFC is involved in the emergence of depression, an important role of the PFC is to adjust the activity within the limbic structure (Andersen & Teicher, 2008). Critically, the PFC does not reach maturity until the early 20s (Giedd, 2004). Thus, the slow developmental process of this region in addition to its complexity, render it particularly vulnerable to the deteriorating effects of stress (Andersen & Teicher, 2008; Russell & McEwen, 2006). Stress-induced remodeling of the PFC results in impairment of attention shifting functions, an important adaptive behavior that is also impaired by lesions to the mPFC.

Moreover, evidence suggests that structures of the PCF are sensitive to remodeling due to prolonged stress and that such remodeling of morphological structures may in part mediate changes in emotionality (Russell & McEwen, 2006). Moreover, the PFC is also vulnerable to the pathology affecting other regions such as the hippocampus or the striatum. As functional properties of the PFC develop progressively, the pathology within the PFC may be silent until the PFC would normally start to regulate the affected abilities (Davey et al., 2008). It is due to this notion, that the PFC has a prominent place in adolescent depression theories such as the triadic model by Ernst, Pine & Hardin, (2006) which notes that the limbic region driving affect matures previous to the cortical structures and as a result regulatory
emotional control is lacking during the adolescent years. However, this mismatch is not highlighted in the continued incidences of depression evident in adulthood (Ernst et al., 2006).

Thus, major depression is suggested to occur due to PFC developmental abnormalities (Andersen & Teicher, 2008). The highlighted view is also supported by adult observations showing decreased orbitofrontal volume in patients with recurrent major depression (Bremner, 2002). Autopsy studies have also shown a significant reduction in density and size of neurons and glia in the dorsolateral and orbital PFC (Andersen & Teicher, 2008). Noteworthy, few morphometric and functional imaging studies have been conducted with an adolescent, the few results that do exist are generally consistent with results seen in adults (Andersen & Teicher, 2008). A study by Botteron, Raichle, Drevets, Heath, & Todd, (2002) noted a reduced left subgenual cingulate volume in middle-aged adults suffering from major depression (MD) \( n = 18 \), but also in adolescents with MD \( n = 30 \). In addition to reduced volume in the right medial frontal gyrus and the anterior cingulate was also seen in teens with MD \( n = 16 \) (Botteron et al., 2002).

Moreover, a longitudinal study conducted by Whittle et al. (2014) noted that attenuation of the normative pattern of PFC thinning during the adolescent period was correlated with inferior emotional and cognitive functioning. The noted study also highlighted links between the abnormal development of the amygdala, hippocampus and the striatum and depressive disorders during adolescence (Whittle et al., 2014). Depressed adolescents also showed increased resting cerebral blood volume (rCBV) in the left orbital and dorsolateral PFC and right subgenual cingulate, as well as the amygdala and the anterior cingulate cortex (sgACC) (Andersen & Teicher, 2008; Blom et al., 2016). Moreover, depressive symptoms
were also related to diminished rCBV in the left PFC and increased rCBV in the right
dorsolateral PFC (Andersen & Teicher, 2008).

Hence exposure to childhood stress over a long period may lead to alteration within
the hippocampal development. As compared to stress during the adolescent years, which are
hypothesized to aid in the development of depressive symptoms by altering the PFC
(Andersen & Teicher, 2008). Exposure to stress during the years of 14-16 activated the PFC
and was related with an 8% synaptic loss by the time of young adulthood (Andersen et al.,
2008). This was also evident in models of social stress on adolescent rats, which lead to an
immediate onset of depressive symptoms. Moreover, MDD in adolescents is often a result of
exposure to one or more stressful life event and may thus be due to stress-induced alterations
within the prefrontal development (Andersen & Teicher, 2008).

Moreover, the amygdala is also often evident in theories concerning depression, this
is based mostly on imaging studies of mood regulation (Andersen & Teicher, 2008). The
amygdala plays an important role in fear conditioning and emotional memory (Russell &
McEwen, 2006). The amygdala has been shown to be over-responsive to fearful stimuli in
participants with MDD in addition to an exhibition of insufficient regulation of PFC control.
This might lead to the persistent degree of negative affectivity, which is a noteworthy and
significant feature of MD (Roberson-Nay et al., 2006). The onset of depression in adolescents
is often foreshadowed by social anxiety, which may be due to over-activation within the
amygdala. Noteworthy, social anxiety typically shows early onset during adolescence and is
rare after the age of 25 years (Andersen & Teicher, 2008). Thus early emergences may be due
to the immature integration of the cortical and limbic components in the expression of
Furthermore, according to Russell and McEwen, (2006) increased cortical involvements in the processing of fearful faces is suggested to be evident, providing potentials means to connect the over-activation of the amygdaloid response. Which has been suggested by preclinical studies, showing delayed connectivity between the basolateral amygdala and the medial PFC (Andersen & Teicher, 2008). Also noteworthy is that the adolescent's amygdala overproduces glucocorticoid receptors (Russell & McEwen, 2006).

Furthermore, replicated findings from fMRI task-based studies demonstrate that adolescents with an MDD show increased sensitivity to stress, indicated by an association between adolescent MD and hyperactivation of the amygdala (Yang et al., 2010). Furthermore, the study conducted by Yang et al. (2010) noted a significantly greater left amygdala activation in un-medicated adolescents diagnosed with MD ($n = 12$; 13-17 years) as compared to the well-matched controls ($n = 12$; 13-17 years). Moreover, the amygdala displays correlative connections with the sgACC, which regulate affective and cognitive processing. Moreover, the subsequent connections also showed hyperactivity in adolescents with MDD, as noted by the study above. Furthermore, the mentioned results highlight that adolescents MDD is characterized by an overactive amygdala response to emotional stimuli, which then further hamper the development of the frontolimbic cognitive control mechanisms and thus contribute to increased social and emotional reactivity displayed by teens with an MDD (Blom et al., 2016; Yang et al., 2010).

3.2 Sex Differences in the Adolescent Brain

According to Andersen et al. (2002), the sex difference apparent in psychiatric illness prevalence rates is mystifying as equally dramatic anatomical differences are not suggested to
be evident. Yet, within this section sex differences within the adolescent brain will be introduced. Furthermore, according to Issler and Nestler (2018), the increase in the prevalence of female adolescent depression occurs in accordance with increases in peripheral estrogen levels during puberty. Hence, the authors suggest that there is an interaction between the effects of circulating ovarian hormones in relation to both sexual differentiation in brain organization and depression susceptibility (Issler & Nestler, 2018). Firstly, sex differences evident in cerebral, cortical and subcortical volume will be introduced followed by sex differences evident within the hippocampus, amygdala, putamen, thalamus, insula, rostral anterior cingulate, superior temporal gyrus, caudate nucleus, caudal anterior cingulate, middle temporal gyrus and inferior occipital gyrus will be highlighted.

Furthermore, often overlooked when examining neuroanatomical changes are the subcortical regions. Nonetheless, these regions undergo some of the largest changes during development. These changes are particularly evident in the basal ganglia in addition to being more pronounced in males (Casey et al., 2005). Conversely, there are noteworthy sex differences apparent in total cerebral volume and females peak before males (11.5 years in females and 14.5 years in males) (Giedd et al., 1999) and according to Lenroot et al. (2007) 10.5 years in females and 11.5 years in males. The size relationship between males and females brains notably varies with age, but on average the male brain is approximately 9% larger during this age span (Giedd, Castellanos, Rajapakse, Vaituzis, & Rapoport, 1997; Naninck et al., 2011) and between 8-10% according to Lenroot et al. (2007). Critically, much of the brain's maturation is accounted for by selective elimination and gross size differences may highlight a variety of different neuronal connectivity and receptor density, the noted differences in total brain size should however not be interpreted as any clear functional advantage or disadvantage. However, these highlighted differences may account for some of
the evident cognitive and behavioral differences displayed by the different sexes during this
time of transition (Giedd et al., 2006).

As already noted, GM volume tends to follow an inverted U developmental
trajectory, GM volume peaked earlier for nearly all structures in girls (Lenroot et al., 2007).
All longitudinal studies that examined cortical GM volume at a lobar level noted that the
maximum GM volume occurs at different times for the different sexes (Giedd et al., 1999;
Lenroot et al., 2007; Naninck et al., 2011). Frontal lobe GM reached its maximum volume at
the age of 11.0 years in girls and 12.1 years in boys, temporal lobe cortical GM peaked at 16.7
years in girls and 16.2 years in boys, parietal lobe cortical GM peaked at 10.2 years in girls
and 11.8 years in boys (Giedd et al., 1999). Lastly, occipital GM volume increased evenly for
both sexes throughout the pubertal age span. Conversely, notable differences can be observed
in cortical GM volume for the different sexes related to specific regions of the brain (Gogtay
et al., 2004). The dorsolateral prefrontal cortex (DLPFC) is involved in the circuitry attending
control of impulses, judgment and decision making. It is notably late to reach adult levels of
cortical thickness. It must be noted that no behavioral implications have been established on
an individual level, however possible political, social and educational implications may be
noted but no clear establishment has been made on this area (Giedd et al., 2006).

Subcortical GM, specifically the basal ganglia consisting of the caudate nucleus,
putamen, globus pallidus, subthalamic nucleus, and substantia nigra have previously been
known to be involved with movement control and muscle tone have lately been suggested to
also be involved with circuits mediating higher cognitive functions and attention in addition to
affective states. Notably, the caudate nucleus is the only structure within the basal ganglia that
has successfully been reliably quantified. Furthermore, alike cortical GM the caudate nucleus
developmental trajectory also follows an inverted U shape (Giedd et al., 2006; Naninck et al., 2011). Critically, the caudate size also shows significant sex differences and is larger in females (Giedd et al., 1997), it peaks at the age of 7.5 years in girls and 10.1 years in boys. However, according to Lenroot et al. (2007), it peaked at around 10.5 for females and 14 for males.

Furthermore, lobar white matter (WM) volume, as compared to GM development, highlight a development course in curves, and also increases throughout childhood and adolescence (Giedd et al., 2006; Naninck et al., 2011). The rate of the increase, however, varies with age the trajectories for the frontal, temporal and parietal lobes, however, are similar (Giedd et al., 2006). The difference between WM and GM growth is alluring, given that the neurons, glial cells, and myelin that entails the GM and WM voxels are contained within the same brain circuitry and have a lifelong complementary companionship (Fields & Stevens-Graham, 2002). So although direct evidence of the hormonal effects of puberty on the anatomy of the human brain is lacking, evidence from clinical populations is starting to suggest specific effects of hormones and/or sex chromosomes on the developmental process and emphasize the importance of not just studying the final destination of brain morphometry, but also the path (Giedd et al., 2006). Noteworthy is again the complexity of any given brain function and within any given region. The daunting complexity of connections, neurotransmitter systems, and synaptic functions makes the desirable straightforward relationship between brain size and function the exception rather than the rule (Giedd et al., 1997; Giedd et al., 2006). Also highlighted differences in the result of Giedd et al. (1999) and Lenroot et al. (2007) is probably due to differences in sample size.
Moreover, within the previous section, the role of the hippocampus in adolescent depression was underlined. Not included was the notion that the hippocampus anatomy is sexually dimorphic, furthermore, the hippocampus is suggested to be a sensitive target for the influence of sex steroids. This sensitivity is attributed to the notion that the hippocampus is highly enriched with estrogen and other steroid receptors (Naninck et al., 2011; Peper et al., 2009). Furthermore, a 10-15% reduction in hippocampal volume were exclusively evident in females with a history of severe and prolonged physical and/or sexual abuse during the childhood years, with MDD. The reduction may be due to alterations in neural plasticity as a consequence of early life stress, which is hypothesized to occur in a sex-dependent manner (Vythilingam et al., 2002).

In a study conducted by Chen, Hamilton, and Gotlib, (2010) they reported evidence of reductions in hippocampal volume in healthy adolescent girls (age 9-15 years). Critically, the noted girls showed evidence of a high familial risk to develop depression as compared to controls with no familial risk. Nonetheless, none of the participants had ever actually experienced a depressive episode themselves yet the reduction in hippocampal volume was already evident in the girls with the high familial risk. Conversely, the study does indicate that the noted reduction in hippocampal volume may precede the depressive onset and instead represent a risk factor. What's more, reduction in hippocampal volume is suggested to be particularly evident in females exposed to early childhood trauma. Moreover, Vythilingam et al. (2002) emphasize the potential consequence of early life stress in females, as a contributor to the development of psychopathology. According to Naninck et al. (2011), the information included above may suggest that early life stress and the prospective hippocampal reductions may serve as a risk factor for the development of stress-related disorders, such as depression and particularly in females.
Moreover, a voxel-based morphometry study conducted by Peper et al. (2009) noted that several brain regions were indeed larger in adolescent boys, they were: the amygdala, putamen, thalamus, insula, rostral anterior cingulate and superior temporal gyrus. On the other hand, the following brain regions were found to be larger in adolescent girls: the hippocampus, caudate nucleus, caudal anterior cingulate, middle temporal gyrus and inferior occipital gyrus (Peper et al., 2009). Furthermore, according to Giedd et al. (2006) in addition to Naninck et al. (2011), several conducted studies have noted that the amygdala volume increases with age in men and that the hippocampal volume increases significantly with age in women. Furthermore, a longitudinal study by Whittle et al. (2014) noted significant sex differences evident in amygdala maturation between the sexes. An increased growth of the amygdala from early adolescence to mid-adolescence in females was linked to the onset of depressive disorders, in addition to a smaller nucleus accumbens volume (across time). Conversely, for adolescent boys, reduced amygdala volume was instead related to the onset of depressive disorders. To conclude, there are indeed sex differences evident within the adolescent brain and the following section will include more in-depth information relating to sex steroids and puberty as such and their impact on the brain.

4. Puberty

Puberty involves successfully altering behaviors, together with the structural brain changes that define adolescence, so that the former child is ready to reproduce and survive independently without the previous level of care and protection from parents and family (Buwalda et al., 2011). This, in turn, results in changes in self-consciousness, identity, and cognitive flexibility. These are all changes enabled by neurochemical and structural maturation within the brain, in areas such as the mPFC which play an important role for the
maturing adolescent (Buwalda et al., 2011). Although there are clear changes occurring within
the brain, few links between these brain-based changes and the behavioral outcome in
addition to the underlying maturational neuroanatomical changes have been clarified
(Andersen & Teicher, 2008). Still unresolved are the questions as to whether the noted
changes are primarily due to maturational events and if so, do they ordinarily act
independently or does a vigorous interplay between hormones and the brain combined
underlie the noted behavioral changes (Andersen & Teicher, 2008; Russell & McEwen,
2006). Moreover, puberty is not a single event but a process that take several years to
complete. Pubertal processes are suggested to occur somewhat earlier in females as compared
to males, as male gonadal development take place 6 months to 1 year later than females (Hyde
et al., 2008).

4.1 Sexual Differentiation and Sex Hormones

Sexual differentiation is the processes by which sex differences emerge and diverge
into male or female phenotypes, adolescence is the period in which sex differences become
more prominent. However, some of these sex differences are evident already in early
development (Naninck et al., 2011; Neufang et al., 2009). A major biological difference
between the sexes is the menstrual cycle. Which causes variations in female sex hormones
(primarily estrogen) over a 28- to 32-day period (Cosgrove, Mazure, & Staley, 2007).
Critically, very little attention has been given to the role of sex steroids, also often called sex
hormones, to the previously discussed differences in brain volumes observed between the
sexes in humans (Naninck et al., 2011; Neufang et al., 2009). By contrast, several studies
using animal models have been conducted and they do suggest volumetric sex differences
within the brain are established in accordance with changed steroid hormone levels during the
developmental years.
Furthermore, the organizational-activational hypothesis (Phoenix, Goy, Gerall, & Young, 1959) does gain consistent support from research using animal models. The hypothesis states that sex steroid exposure during prenatal and early postnatal development sexually differentiates the neural circuits’ organization, which then is activated in early adulthood by sex steroids leading to the emergence of sex-typical behavior. However, according to Naninck et al. (2011), the debate concerning the hormone-driven sexual differentiation of the brain during different developmental periods has not yet reached its end. New evidence highlight that the organizational effect of sex steroids are not limited to a specific sensitive period but that such changes can also occur during the adolescent period when exposure to sex steroids can alter the brain in a sex-specific manner. Additionally, sex steroids and neurotransmitter systems are linked in multiple ways, yet, there interaction is so complex that it remains hard to study (Naninck et al., 2011).

### 4.2 Sex Hormones and Adolescent Depression

However, according to Andersen and Teicher, (2008), there are 3 sets of maturational factors that promote the origin of adolescent depression. The first one is the maturational changes that occur within the adolescent brain thus including anatomical and functional rearrangements, sensitivity to gonadal and adrenal hormones in addition to the increased psychosocial pressure that continuously increases during this transitional period as the social milieu of the adolescent world grow in depth and complexity. The second factor is windows of vulnerability, occurring within the different brain regions at different times, thus leaving the brain, less or more susceptible to environmental influencers that may increase the risk of developing depression. The third factor is maturational changes that lead to the overt expression of the disorder in individuals with an already underlying predisposition (Andersen
& Teicher, 2008). Moreover, according to Hyde et al. (2008) the rise in adolescent female depression may be linked to the pubertal rise in adrenal androgens (DHEA and DHEAS), sex steroids (estrogen, progesterone, and testosterone) and/or the gonadotropins (FSH and LH).

In girls, the onset of menarche results in monthly fluctuations in levels of gonadal hormones and gonadotrophins. Adolescent girls’ also experience a rapid increase in estrogen levels which corresponds with an up-regulation in HPA-axis activity, moreover, these alterations combined may lead to increased levels of negative mood in adolescent girls. Hence the onset of cyclic fluctuations in sex hormones may be linked to the increased rates of depressive symptoms in adolescent girls (Naninck et al., 2011). Furthermore, evidence of a threshold effect has been noted, so that the rising of hormones may not have any effect on behavior until they reach a certain level. Moreover, the relationship between baseline circulation of hormones and behavior are indicated to be non-linear. Levels of hormones are accentuated to play an important role in the organization and activation of the brain as they alter the brain structural development, resulting in altered functional properties. An example being the effect of gonadal hormones on the organization, which is evident during the prenatal period as this is when sexually dimorphic parts of the central nervous system arise. Later during puberty, gonadal hormones are highlighted to play a role in brain maturation and thus shaping cognition, mood, and behavior (Walker, 2002).

Critically, some of the normal brain changes evident in human adolescents are emphasized to occur due to hormones altering the expression of genes that in turn guide maturational processes such as proliferation and elimination of neuronal processes. This then raises the possibility that hormonal changes also potentially trigger genes during adolescence that contribute to the onset of emotional vulnerability (Walker, 2002; Watson & Gametchu,
The post-pubertal increase in heritability which is evident may be due to hormonal maturation resulting in the engagement of genes that were previously silent. Thus, if an individual already possesses these vulnerability genes, then the sign of a behavioral disorder may not become evident until triggered by gonadal and adrenal hormones. An example of this is the rise in hormones during puberty which then, in turn, trigger the gene which codes for abnormal dopamine neurotransmission, potentially then in turn giving rise to brain abnormalities increasing susceptibility to schizophrenia (Walker, 2002). This may be similar for the vulnerability to depression, which may be a result of hormone surges triggering the potential vulnerability genes that in turn leads to deficits in one of the highlighted neurotransmitter systems involved in depression, such as the serotonin system. It is also possible that insufficient levels of gonadal and adrenal hormones lead to failure in gene expression important for brain maturation, leading to psychopathology. Behavioral adjustment problems may arise during puberty as a result of the activation of the preexisting abnormality within this brain region. Thus a previously silent brain lesion could begin to negatively influence the behavior during the onset of puberty (Walker, 2002).

Moreover, the brain displays regional differences in the trajectory of synaptic development highlighted by different rates of myelination, connectivity between different brain regions, the increased expression of glucocorticoid receptors and the programming of neuropathic factor levels thus all potentially conclude in brain region-specific windows of vulnerability. This occurs at different ages and thus overall increase the sensitivity to the onset of depression during the adolescent years. Furthermore, males typically overproduce synapses and signaling mechanism more than females, this may be due to sexual dimorphism (Giedd et al., 1997). As already mentioned, females peak in GM density 1-2 years before males (11.2 versus 12.6 years), it is the fetal exposure to gonadal hormones that may wield the effects
responsible for the sex differences apparent (Lenroot et al., 2007). It is the pubertal exposure that activates the hormones which then modulate the development of the PFC, amygdala and the hypothalamus. However, the role of gonadal hormones in this process is not yet clear-cut and continued research is needed (Giedd et al., 2006; Naninck et al., 2011). If we, however, look to rodent studies, it is suggested that estrogen suppresses the neuronal overproduction within specifically the female PFC whereas high levels of testosterone, on the other hand, appear to aid in the pruning of dendrites in the male amygdala (Markham, Morris, & Juraska, 2007). Furthermore, adolescence as such is associated with sexually dimorphic pruning of synapses and signaling mechanisms, in regions of the brain implicated in the development of depression. Thus, the emergence of depression might be due to either insufficient overproduction or enhanced pruning within the specific brain regions (Andersen & Teicher, 2004).

Furthermore, according to Andersen and Teicher, (2008) gonadal hormones are highlighted to mediate their effect obliquely through GABA, 5-HTTLPR and/or the dopamine systems which are all differently involved in anxiety and depression. Notably, stress-related hormones (such as glucocorticoids and mineralocorticoids) also play an important role in molding the brain, as they aid in the programming of adaptive functions and synaptic selection. Their role, however, may occur through epigenetic mechanisms or through the regulated expression of various genes. An excess of the hormones mentioned, and specifically glucocorticoids (GC) can alter the brain effectively by changing trajectories of development that are predisposing to the emergence of psychopathology as such (Wei et al., 2004).

Mood as such is regulated by the interaction between the cortical and limbic regions, and as these pathways mature they are specifically vulnerable to the exposure of gonadal and
adrenal hormones. Episodes of melancholic depression are often accompanied by increased levels of GC secretion, potentially suppressing hippocampal neurogenesis. Yet, whether GC is the cause or the consequence of emotional dysregulation is not yet clear and needs further investigation (Sheline, Gado, & Kraemer, 2003). However, it has been suggested that adolescents may be increasingly vulnerable to stress exposure due to GC receptor expression in the cortex in addition to a more prolonged and exacerbated corticosterone response following acute stress. Female rats display an increased GC response to stress compared to male rats, which may explain the increased susceptibility to the learned helpless displayed by the female rats (Russell & McEwen, 2006). Thus, increased vulnerability to stress may be a key contributing factor to the increased occurrence of depression among adolescents. Acute stress may precipitate in the onset of the disorder in individuals with an already vulnerable predisposition (Andersen & Teicher, 2008).

5. Stress and Adolescent Depression

Discussed within the previous sections were the complex interplay between the brain, hormones, and stress. However, due to the complexity within all the mentioned systems in addition to their combined interactions, it is troublesome to differentiate between the impacts of hormones, genes, and stress (both separately and their interaction) on brain maturation in addition to their effect on the emergence of depressive symptoms. Hence, the role of sex steroids on stress sensitivity and mood need further investigation. Within this section the role of stress in the onset of the 2:1 ratio will be emphasized. Critically, physical and social stress in humans shows strong ties to the life-long development of psychopathologies. This assumption comes from a large number of studies, highlighting stressful life events as increasing the probability of the development of depressive symptoms in adolescence, but also during other phases of life (Andersen & Teicher, 2008; Blom et al.,
Whilst there may be an underlying genetic predisposition to stress sensitivity and an overactive HPA-axis, it is, however, outside the scope of this essay to examine the genetic component of stress sensitivity. The next section will discuss research concerning one of the body's major stress systems and notable sex differences evident.

5.1 HPA-axis Functioning and Stressful Life Events

The HPA-axis is one of the body's major stress systems and the dysfunction of the HPA-axis has most persistently been linked to depression (Burke, Davis, Otte, & Mohr, 2005; Walker, 2002). The HPA axis includes the hypothalamus, pituitary, and adrenal gland and has a central role in biological stress responses (Walker, 2002). A noteworthy role of the HPA axis in adolescent depression is that it controls the rise in sex hormones (estrogen and testosterone). Again the heterogeneous nature of depression must be noted which may conceal the possible pathway from which stressful life events lead to the generation of depressive symptoms. However, studying the endophenotypes of depression could partly unravel this seemingly daunting mystery. The HPA-axis appear to be a valid endophenotype as suggested by an increased sensitivity to the depressogenic property of stressful life events (Oldehinkel & Bouma, 2011).

The gonadal steroid hormones released by the HPA-axis does shape the brain neural circuitry and by doing this modifies social behavior and skills, which are most important during this increasingly socially complex milieu and for adult reproduction (Oldehinkel & Bouma, 2011; Walker, 2002). These changes also alter the way the individual interacts with the opposite sex, as the individual transforms from being primarily interested in same-sex relations to experiencing a growing interest in romantic relationships (Buwalda et al., 2011).
Furthermore, as compared to prepubertal children, recent evidence suggests that adolescents demonstrate an over-activity in the HPA-axis due to social stressors (Stroud et al., 2009). HPA-axis reactivity has been shown to be heritable, as healthy family members to depressed individuals also show an altered HPA-axis response to stress (Federenko, Nagamine, Hellhammar, Wadhwa, & Wust, 2004). Thus, it is often assumed that the HPA-axis serves as a mediating link between stressful life events and different subtypes of depression (Oldehinkel & Bouma, 2011).

5.2 The Maturing Brain and Stress Reactivity

Depression is considered to be a stress-related disorder, stress and stress-sensitivity are generally believed to play an important role in the etiology of depression (Andersen & Teicher, 2008). Although much research has been conducted on the effects of stress and stress hormones on structure and function of the prenatal brain, less is known about the impact of stress and stress hormones on the pubertal brain (Russell & McEwen, 2006). Stress-related hormones such as glucocorticoids (GC) are suggested to have a key role in sculpting the adolescent brain (Pryce, 2008). Furthermore, exposure to early life stress in addition to lack of social bonding and support can lead to detrimental effects on the central nervous system and this, in turn, can lead to increased vulnerability to depression (Blom et al., 2016).

The question is if the high structural neuronal plasticity associated with the period of adolescence leads to increased sensitivity to the detrimental effect of stress. Brain areas involved with affective and cognitive regulation, critical for handling the aforementioned stressor, undergo both functional and anatomical reorganization through increased myelination and synaptic pruning during the adolescent years (Giedd, 2004). Although this is widespread within the brain, it is concentrated particularly within the PFC (Gogtay et al.,
As already mentioned the PFC plays a central role in regulating the hypothalamic and amygdala response to psychosocial stressors (Oldehinkel & Bouma, 2011). The PFC is targeted by the effects of stress. Rodent models suggest that repeated stress shortens the overall length of and reduces the number of branches of dendrites in the PFC, indicating that the brain circuits under construction during adolescence are indeed more sensitive (Buwalda et al., 2011). Thus, it is possible that the ongoing maturational changes play a role in why the brain appear extra sensitive to stressful experiences during the adolescent period of life, as compared to all other periods (Oldehinkel & Bouma, 2011).

Although there are many important features of stress, it is outside the scope of this essay to discuss them all. However, two stressors that have consistently been tied to the onset of adolescent depression are aversive childhood experiences (ACEs) and parental depression. In this section ACEs will be introduced, ACEs are a major risk factor in the development of psychopathology. ACEs encompass abuse and adversities that can be of physical, sexual, emotional or psychological nature, with each type having been separately associated with the development of depressive symptoms (Andersen et al., 2008; Chapman et al., 2004). If early childhood adversity results in morphological change and the extent of such, and/or the onset of depression is likely determined by genetic susceptibility, severity, frequency and the profusion of the stressor as such, but gender and timing are also important factors (Andersen et al., 2008; Oldehinkel & Bouma, 2011). In a study conducted by Chapman et al. (2004) a strong graded relationship was evident between the number of ACEs and recent and lifetime episodes of depressive symptoms for both men and women. The study also reported higher numbers of ACE in women in addition to increased depressive rates. These results highlight the deteriorating effects of abuse on the mental health of the victim and implicate the prevalence of ACEs as a strong predictor of depressive symptoms (Chapman et al., 2004).
Furthermore, physical or sexual abuse have been highlighted to alter brain structure including altered left hemisphere maturation, diminished size of the corpus callosum, reduced hippocampal volume in adults (but not children), changes in GM volume, symmetry and neuronal integrity of the frontal cortex and lastly reduced size of both the anterior cingulate cortex and the caudate nucleus (Oldehinkel & Bouma, 2011). Many of the region mentioned are involved in emotional regulation and similar abnormalities can be found in individuals with depression. However, it must be noted that this is a new area of research and although several cross-sectional studies reported morphological differences, enough evidence for a cause and effect relationship has not yet been established (Oldehinkel & Bouma, 2011).

The next section will focus on parental depression. Parental psychopathology is the strongest predictor of the onset of depression in children and adolescents, likely due to genetic influence, environmental influences or a combination of both. It is likely that the developmental pathway is set up by an interaction between genetic predisposition and an environment triggering such. Adoption studies have suggested that both factors are at work. However, the impact of parental psychopathology is most likely complex and is part of a cluster of factors such as family violence, neglect, abuse and other types of childhood adversities (Kessler et al., 2001). Epidemiology studies have emphasized that parental depression predicts offspring depression, with children of depressed parents being three times more likely to develop major depressive symptoms than children of non-psychiatric controls. Children of depressed parents display a lifetime risk of developing depression by up to 45%. Furthermore, family history of depression also aided the prediction of recurrent episodes, suggested by a prospective study (Miller, 2007).
The noted potency of parental, and particularly maternal depression, as a risk factor for the development of depression in youths, is well researched and its effect has been demonstrated in many research reports (Oldehinkel & Bouma, 2011). High frequency of specifically maternal aggression and low frequency of maternal positive behaviors, predicted the onset of major depression in adolescents (Schwartz et al., 2017). Parental depression is suggested to amplify a variety of risk factors such as negative emotionality, dysregulated aggression, cognitive vulnerability factors, poor academic performance in addition to HPA-axis and cortical activity (Oldehinkel & Bouma, 2011). According to Goodman and Gotlib, (1999) and reviewed by Goodman, (2007), four maladaptive mechanisms are highlighted in relation to maternal risk factors of depression and thus the related transfer to their offspring: exposure to maladaptive maternal cognition, behaviors and affect, exposure to a stressful environment in addition to heritability. These four mechanisms have been extensively reviewed and considerable evidence has been accumulated for each pathway. As already noted, genetic factors also account for a substantial proportion of the deviation in depression, supported by findings highlighting that children born to depressed mothers display neuroregulatory dysfunction (Goodman, 2007).

5.3 Sex Differences in Stress Reactivity

A growing number of studies suggest that the association between depression and stressful life events are stronger in females as compared to males (Aube et al., 2000; Bouma et al., 2008). As already mentioned, this sex difference first appears during the adolescent years. Moreover, this is further accentuated by evidence highlighting that parental divorce was associated with stronger depressive symptoms in middle-aged adolescent girls as compared to middle-aged adolescent boys and in comparison with younger adolescents of both sexes. The effects of divorce appeared similar at the age of 10 for both sexes, the
difference appeared during the subsequent years. Girls became increasingly sensitive to the effects of divorce, while no modified effect was seen in relation to age in boys (Silberg et al., 1999). The noted difference between the sexes may be due to different actions of male and female sex hormones, gonadal steroid hormones’ interact with receptors in the brain and the adrenal glands. This potentially contributes to the notable sex difference in stress reactivity with respect to both physiological stress systems and cognition involved in psychological coping with the stressor (Abela & Hankin, 2008).

Notably, in humans, the cortical brain regulating hypothalamus and the amygdala is still developing during the adolescent years and shows sexual dimorphism regarding its function, morphology and developing trajectories (Cosgrove et al., 2007). Thus, the adolescent years is emphasized by changing gonadal hormone levels within the developing brain and it has been suggested that this complex interplay likely affect stress response differently within the sexes. In animals studies, sex differences in relation to stress are the norm rather than the exception, however, the difference in nature depends on the type of stressor (Gillies & McArthur, 2010). An example being that chronic stress induces hippocampal deficits in male rats, but conversely, enhance memory functions in female rats. A notable contrast is that acute stress instead lead to enhanced learning in male rats, but impaired learned in female rats. However, it is not clear if the mentioned result is at all generalizable to humans (Oldehinkel & Bouma, 2011).

Sex differences are also apparent in HPA-axis response, it has previously been theorized that girls suffer from an increased risk of developing depression due to dysregulation of the HPA-axis. This as physiological stress responses are suggested to be altered by increasing levels of gonadal hormones (Weiss et al., 1999). Sex differences in
stress response have been proposed to be responsible for some of the sex difference seen in depression (Stroud, Salovey, & Epel, 2002). Moreover, findings from both animal and human studies suggest that the HPA-axis is influenced by female sex hormones and that this sex difference again emergence during the adolescent years (Gillies and McArthur, 2010). The female sex hormone is hypothesized to alter cortical receptors in the hypothalamus and amygdala directly and also through regulating functions (Turner, 1997). High levels of estrogen have been highlighted to enhance the efficacy of serotonin transporters in such a way that it generates increased serotonergic neurotransmission in the brain (Oldehinkel & Bouma, 2011). Progesterone, on the other hand, can diminish the HPA-axis feedback through binding on to cortisol receptors (Turner, 1997). However, these mechanisms specifically need further research conducted with humans.

Furthermore, the nature of the stressor also alters the stress response. Again, men demonstrate an increased cortisol response due to achievement stress, while females show the same pattern in relation to social rejection, once more emphasizing the increased sensitivity to interpersonal stress for females. In line with these findings, Stroud et al. (2002) suggested that the increased sensitivity to rejection stress in females may be in part responsible for increased rates of depression among women. Noteworthy, a study conducted by Bouma et al. (2008) showed that parental depression not only increased the risk of developing depression but also predicted the cortisol release in response to social stress, significantly in girls’ but not boys. Furthermore, daughters of a parent with a notable history of depression displayed blunted cortisol response, while daughters of parents with no such depressive history did not. A blunted cortisol response which entails a down-regulation of the HPA-axis, can at times be adaptive but it has also been associated with stress-related disorders (Bouma et al., 2008). Again, these results need further replication. However, similar results have been found when
examining startle reactivity in offspring of individuals with a depressive disorder, showing that granddaughters, but not grandsons, also exhibited elevated startle response (Oldehinkel & Bouma, 2011).

Furthermore, as already noted, females are exposed to different types of stressors than males. A study conducted by Kendler et al. (2001) on adult twins suggested that females experienced more interpersonal stressors than males, but males, on the other hand, experienced more legal and work-related stressors. This pattern was also found in a study by Rudolph and Hammen, (1999) conducted on adolescent, where boys a appeared more sensitive to academic-failure and trouble with police were girls, on the other hand, again reported increased interpersonal stress related to peers and parents. Another study conducted by Oldehinkel, Rosmalen, Veenstra, Dijkstra, and Ormel, (2007) noted that depression in girls was strongly linked to a low affection-related status - not being liked by peers, were boys, on the other hand, were more sensitive to low achievement related status such as not being good at sports. The mentioned findings above suggest that adolescent girls experience increased sensitivity to the depressogenic effect of dysfunctional interpersonal relations, while adolescent boys, on the other hand, are more affected by situations that may threaten their status within the peer group (Oldehinkel et al., 2007). A comparable result was also found within a large Dutch sample of adolescents suggesting that the sexes were exposed to different individual stressors, but also that the sexes reacted differently to them. Thus highlighting that general stress measures do not reflect the same experiences (Bakker, Ormel, Lindenberg, Verhulst, & Oldehinkel, 2010). Consistent with previous results Comasco and Nordquist, (2008) found that adolescent girls reported more depressive symptoms due to family stress and that adolescent boys reported more depressive symptoms due to school stress (Oldehinkel & Bouma, 2011).
6. Models and Theories of Adolescent Depression and the Emerging 2:1 Ratio

Depression is an exceedingly complex illness with several etiologies, including genetic, epigenetic and environmental factors which altogether lead to the development of the disorder (Dean & Keshavan, 2017). The disorder has several pathophysiological mechanisms and progress within the field of depression has been slowed down by the tendency of different schools of thought to fight for their specific pathophysiology of depression. Further, the mistake of seeing one small part of the disease as the disease itself results in the larger picture often being overlooked. The bigger picture, in this case, is that most psychiatric disorders are an interactional matrix of a multitude of factors, therefore the disease cannot be reduced to a single factor alone (Dean & Keshavan, 2017; Hyde et al., 2008). Thus, the complexity of depression calls for models leaving simplifications behind, as no one factor can account for the development of depressive symptoms in a large variety of individuals (Dean & Keshavan, 2017). Due to the primary focus of this essay on the emergence of 2:1 ratio during adolescence, models, and theories that aid the understanding of key factors that may generate the 2:1 ratio during adolescence will be included. Critically, the information included here will only continue to highlight the already introduced areas of neurodevelopmental change, hormonal factors, and stress.

Critically, the emergence of sex difference in depression during adolescence has attracted the attention of many, thus, its origin has been attributed to a wide variety of factors (Hyde et al., 2008), some of which were presented in the introduction section of this thesis. Considering this, Hyde et al., (2008) suggest that a theory that proposes only a single developmental pathway of adolescent depression or the 2:1 ratio of female depression, is doomed to be contradicted by data. Thus, it is clear that there are multiple pathways to
adolescent female depression (Hyde et al., 2008). The affective, biological and cognitive (ABC) model emphasize the following factors, genetic vulnerability, pubertal timing and temperament, and negative cognitive style and negative life events. These, factors all represent dimensions of individual differences and therefore, combined they should explain within-sex variability in depression onset in addition to sex differences in depression prevalence. Although the ABC model continuously emphasizes its integrative strength it severely lacks information concerning the brain. Highlighting a great problem with current theories and model concerning the origin of sex differences in adolescent (Hyde et al., 2008). The problems are the lack of attention given to the sex differences evident within the brain and the brains ongoing maturation in affiliation with depression onset and sex differences in prevalence (Whittle et al., 2014).

Following, the role of the brain in adolescent depression and in the emergence of the 2:1 ratio of female depression will now be highlighted. As previously suggested, there are significant sex differences evident in brain maturation and in volume within cerebral, cortical and subcortical regions of the brain. However, there is currently no clearcut answer to how and if, these sex-based brain differences in volume aid the development of adolescent depression and the onset of the 2:1 ratio (Giedd et al., 1997; Giedd et al., 1999; Giedd et al., 2006; Lenroot et al., 2007; Peper et al., 2009), no definite conclusions about its association can currently be made. However, a review of neuroimaging studies conducted by Kerestes et al. (2014) noted an abnormal activation in the ventromedial and orbitofrontal frontal regions, the amygdala and the anterior cingulate in adolescents suffering from depression. Moreover, a study conducted by Whittle et al., (2014) found that attenuation from normative patterns of development in the hippocampus, putamen and amygdala volumes (the latter for males only) from the age of 13-16 years, was associated with the onset of depressive episodes in the
adolescent. For females, the study found that accelerated growth of the amygdala from the age of 12-16 years, in addition to a smaller nucleus accumbens volume (across time) was associated with depression onset. The marked sex differences in the association between changes in amygdala volume and depression onset, contribute to our understanding of the role of sex differences in brain development and its association with the 2:1 ratio and the timing of general depression onset. Hence, the abnormal maturation of crucial brain areas may precede the onset of depression, thus representing a significant vulnerability factor (Whittle et al., 2014).

Furthermore, the imbalance between the late maturing PFC and the early maturing limbic region has continually been emphasized to play a role in the development of adolescent depression (Andersen & Teicher, 2008; Blom et al., 2016; Casey et al., 2008; Davey et al., 2008; Nelson, Leibenluft, McClure, & Pine, 2005; Sturman & Moghaddam, 2011). This is specifically highlighted within the model of the social information processing network, which emphasizes the mismatch between the cortically based cognitive-regulatory region versus what the author referred to as the affective node, which is suggested to be equivalent approximately to the subcortical limbic system (Nelson et al., 2005). The triadic model by Ernst et al., (2006) also highlight the imbalance between regulatory parts and affective parts, through suggesting that the development of the approach system precedes the maturation of the avoidance system (Ernst et al., 2006). Although the imbalance between the noted brain areas is a vital contributing factor to the onset of adolescent depression (Davey et al., 2008; Ernst et al., 2006; Nelson et al., 2005), no statement in relation to sex differences is currently possible.
An area where sex differences as such are given the appropriate attention is research concerning puberty and sex hormones and their role in adolescent depression and specifically, the greater prevalence of depression among adolescent girls (Andersen & Teicher, 2008; Angold et al., 1998; Goodyer et al., 2000; Halbreich & Kahn, 2001; Hyde et al., 2008; Naninck et al., 2011; Patton et al., 1996; Steiner et al., 2003; Walker, 2002). Furthermore, the timing of the emergence of sex differences in adolescent depression, around 13-15 years of age, implicates pubertal processes. Puberty as such is not a single event, but a process that occurs over several years and the end results is an adult appearance and physiology (Hankin & Abramson, 2001; Hyde et al., 2008). Moreover, according to Girgus and Yang, (2015) biological, physical and psychological changes increase in line with pubertal changes. Furthermore, the biological changes that occur are coordinated by increasing levels of sex hormones. However, sex hormones independently are not suggested to increase the risk of developing depression during adolescence, rather it is the early onset of puberty that has consistently been attributed to confer increased risk of developing depression symptoms (Angold, Costello, Erkanli, & Worthman, 1999; Girgus & Yang, 2015; Hamilton, Hamlat, Stange, Abramson, & Alloy, 2014).

Moreover, the results from a large Finish study noted that puberty occurs somewhat earlier in females as compared to males. Furthermore, the results noted that 51% of females had experienced menarche before the age of 13 years, as compared to 38.4% of boys had experienced oigarche (i.e., age of the first ejaculation), before the age of 13 years. Furthermore, the study also suggested that early puberty was associated with increased depression in both sexes (Kaltiala-Heino, Kosunen, & Rimpelä, 2003). However, previously conducted research on the area only found a connection between early pubertal onset and increased depression, in adolescent females (Essau et al., 2010; Girgus & Yang, 2015; Hyde
et al., 2008; Seiffge-Krenke & Stemmler, 2002; Stice, Presnell, & Bearman, 2001). Moreover, according to Girgus and Yang, (2015) several factors account for the increased risk of developing depression due to early pubertal onset in adolescent females, firstly the onset of puberty may be associated with physical changes that are negatively perceived by adolescent girls. Secondly, early puberty may be correlated with an earlier engagement of sexual activity, which has been suggested to be tied with elevated risks of stress and depression. Thirdly, early onset of puberty may interact with stressful life events to produce an increased risk of developing depression (Girgus & Yang, 2015). Furthermore, the interaction hypothesis suggests that pubertal timing is indeed a vulnerability that interacts with stressful life events to increase the risk of developing depression (Ge, Conger, & Elder, 2001). Moreover, after the age of 13 years, both sexes are found to report more overall negative events. This developmental increase in the number of negative events starting after puberty closely parallels the surge in depressive episodes (Hankin, 2015; Hankin & Abramson, 2001). Moreover, the gonadic theory by Oldehinkel and Bouma, (2011) emphasize that the hormonal levels of females fluctuate cyclically over a much larger range than those of men and that this increased hormonal fluctuation may affect brain regions involved with the modulation of mood and behavior (e.g., PFC and the hippocampus). Moreover, the theory emphasizes the interplay between estrogen and glucocorticoids and suggest that fluctuations within estrogen levels may render females increasingly vulnerable to the effects of stress and also the onset of depression (Faravelli et al., 2013; Oldehinkel & Bouma, 2011).

Stress and depression have often been highlighted to be related and this is also the case with depression emerging during adolescence (Andersen & Teicher, 2008; Blom et al., 2016; Buwalda et al., 2011; Hankin, Mermelstein, & Roesch, 2007; Kendler et al., 2001; Patton et al., 1996). Furthermore, this is highlighted by the notion that stressful life events can
aid in the generation of depressive episodes in individuals already vulnerable, but also by the notion that childhood stress in the shape of abuse or neglect does increase the risk of developing depression later in life (Buwalda et al., 2011; Chapman et al., 2004; Hankin, 2015; Oldehinkel & Bouma, 2011; Russell & McEwen, 2006). Furthermore, females report more overall stress and negative events (Hyde et al., 2008), in addition to displaying a stronger association between stressful life events and depression (Essau et al., 2010; Oldehinkel & Bouma, 2011). Moreover, Hankin et al. (2007) emphasize two models that may explain why girls experience more depressive symptoms after puberty. Furthermore, according to the mediational-stress exposure model, adolescent girls experience more stressors overall than boys and as a result, girls become more depressed. However, according to the mediational-stress exposure model girls instead experience greater levels of depression as a result of stress, as compared to boys (Hankin et al., 2007).

Furthermore, abnormalities of the HPA-axis has been found in individuals suffering from depression, such as a hyperactive HPA-axis response to stress (Dean & Keshavan, 2017; Oldehinkel & Bouma, 2011). Critically, Weiss et al., (1999) theorize that adolescent girls do indeed suffer from an increased risk of developing depression due to dysregulation of the HPA-axis in a sexually dimorphic way. The sex differences in stress response and activity of the HPA-axis have been continuously highlighted to in part contribute to the 2:1 ratio evident (Gillies and McArthur, 2010; Naninck et al., 2011; Stroud et al., 2002; Weiss et al., 1999). Moreover, the depressogenic diathesis states that risk factors such as insecure attachment to parents, anxious-inhibited temperament and low instrumental coping skills independently and interactively contribute to the emergence of the 2:1 ratio during adolescence. Critically, the noted risk factors may be evident prior to puberty in addition to being manifested by both sexes. However, the depressogenic diathesis states that after puberty the noted risk factors
may constitute an increased risk for specifically adolescent girls due to alteration within the social and hormonal milieu after puberty (Cyranowski et al., 2000).

To conclude, to focus on only one of all the mentioned mechanisms as the main cause of depression is clearly too reductionistic. Instead, all of the highlighted mechanisms are suggested play a role in the complex interactive matrix that is pathological factors (Dean & Keshavan, 2017). Thus, all the factors highlighted in this section have their own role to play in the adolescents’ developmental journey towards depression and the increased prevalence in females. However, although the final destination is somewhat the same (depressive episode) the unique developmental pathway to the end destination, can vary to a great extent (Hyde et al., 2008).

7. Discussion

Before all else, an admittedly selective focus is present within this essay. Thus, included within the essay is research that emphasizes sex differences in brain maturation, pubertal and hormonal influences in addition to stress and different stressors that may aid the emergence of the 2:1 ratio during the transitional period. Thus, the theories and models that are highlighted in this section are included due to their consistent support by research introduced previously. However, due to the selective focus of the essay, the models or theories introduced here are not emphasized to completely or independently explain the emergence of the 2:1 ratio during the transitional period. However, united the theories or models emphasized here may generate an increased understanding of the key contributing factors that contribute to the onset and the timing of the 2:1 ratio.

Currently, the most consistently emphasized factors that potentially contribute to the development of the 2:1 ratio during adolescence are hormonal influencers such as pubertal
onset (Andersen & Teicher, 2008; Angold et al., 1998; Goodyer et al., 2000; Halbreich &
Kahn, 2001; Hyde et al., 2008; Naninck et al., 2011; Patton et al., 1996; Steiner et al., 2003;
Walker, 2002), in addition to an increased reactivity and sensitivity to stress, displayed by
adolescent girls (Andersen & Teicher, 2008; Blom et al., 2016; Buwalda et al., 2011; Hankin
et al., 2007). Hence, within the following section, I emphasize hormonal and stress-related
factors that interact and combined are indicated to contribute to the onset of the 2:1 ratio.
Furthermore, the gonadic theory by Oldehinkel and Bouma, (2011) emphasize females
increased sensitivity to depression may be due to an increased cyclic span of hormonal
fluctuations (Oldehinkel & Bouma, 2011). Moreover, these increased cyclic hormonal
fluctuations are also hypothesized to affect brain regions involved with the modulation of
mood and behavior (e.g., the PFC and the hippocampus) (Faravelli et al., 2013). Additionally,
the theory also emphasizes the interplay between estrogen and glucocorticoids and highlight
that fluctuations within estrogen levels may lead to increased female vulnerability to the
effects of stress and the onset of depression (Faravelli et al., 2013; Oldehinkel & Bouma,
2011). In line with this, the depressogenic diathesis also suggests that females increased
vulnerability to depression may be due to changes in the social and hormonal milieu after
puberty that render adolescent girls particularly vulnerable to psychological risk factors such
as an insecure attachment to parents (Cyranowski et al., 2000).

Critically, according to Oldehinkel et al. (2007) and Rudolph and Hammen, (1999)
females are indeed suggested to demonstrate a rising vulnerability to interpersonal stress after
puberty (Aube et al., 2000; Oldehinkel et al., 2007; Rudolph & Hammen, 1999). Combined
with an increased dependence on relationships and affective needs (Cyranowski et al., 2000).
Moreover, according to Hankin et al. (2007) the relationships of adolescent girls as compared
to boys, were suggested to be characterized by elevated levels of intimacy, emotional support,
and self-disclosure. Furthermore, girls also displayed a stronger association bounded by close interpersonal relationship and feelings of identity and self-definition. This, increased female sensitivity is further accentuated by the notion that parental divorce was associated with stronger depressive symptoms in adolescent girls as compared to adolescent boys. Moreover, at the age of 10 years old the effects of divorce were equal between the sexes, however, during subsequent years the girls displayed an increased sensitivity to divorce while no such increase was displayed by the boy (Silberg et al., 1999). Thus, support for the depressogenic diathesis may be noted by the research mentioned above, which suggest that after puberty females place an increasingly greater value on interpersonal relations in addition to being more affected by dysfunctional interpersonal relationships.

Moreover, the interaction hypothesis also suggests that pubertal timing is a vulnerability factor that interacts with the stressors and combined they increase the risk of developing depression (Ge et al., 2001). Furthermore, in a study conducted by Ge et al. (2001), the early-maturing adolescent females represented the group with the highest rates of depression. Critically, the findings also suggested that the early-maturing girls with more initial symptoms in addition to more recent stressors were the most likely group to be depressed. Again emphasizing the crucial interaction between psychosocial factors and an early pubertal onset, thus this interaction might represent a valid risk factor that significantly contributes to the development of depression. In addition, to potentially contributing to the timing of the emerging 2:1 ratio during puberty (Ge et al., 2001).

Critically, after puberty females do indeed report more overall stress and negative events (Hyde et al., 2008), in addition to displaying a stronger relationship between stressful life events and depression (Essau et al., 2010; Oldehinkel & Bouma, 2011).
noted above also support the moderational-stress reactivity model, which states that girls exhibit greater levels of depression as a response to stress. Moreover, according to Weiss et al. (1999) girls suffer from an increased risk of developing depressive symptoms due to dysregulation of the HPA-axis in a sexually dimorphic manner. Furthermore, the mediational-stress exposure model draws support from the notion that females do indeed experience more overall stressors, moreover, the model proposes that as a result of experiencing more overall stressors, adolescent girls subsequently suffer from increased depression rates (Hyde et al., 2008).

The authors Abela and Hankin, (2008) hypothesize that the differences in stress sensitivity and reactivity between the sexes may be due to the different actions of male and females gonadal steroid hormones. Furthermore, Cosgrove et al. (2007) suggest that the complex interplay between changing levels of gonadal hormones within the developing brain may alter the function, morphology of the developing trajectories of the cortical brain that regulate the hypothalamus and the amygdala. Thus, the complex interplay between changing levels of gonadal hormones and brain development evident during the transitional period, likely affect stress response differently in the sexes.

Moreover, to the best of my knowledge, there is currently no theory or model that take into account sex differences in brain maturation and emphasize potential behavioral implications due to those differences, in addition to somewhat contribute to the understanding of the onset of the 2:1 ratio. Research investigating neurodevelopmental risk factors that potentially contribute to the onset of depression during the adolescent years have grown in number. Currently, the available articles that I suggest contribute the most to the increased understanding of the neurodevelopmental factors that potentially aid the development of the
Moreover, key neurodevelopmental changes that potentially aid the development of the 2:1 ratio will now be emphasized. Critically, mood as such is regulated by an interaction between cortical and limbic regions and as these pathways mature they are sensitive to the exposure of gonadal and adrenal hormones (Sheline et al., 2003). Furthermore, the cortical brain that regulates the hypothalamus and the amygdala is still maturing during the transitional period, moreover, it is hypothesized to be sexual dimorphism regarding its function, morphology and developing trajectories (Cosgrove et al., 2007). Additionally, adolescent transitioning is correlated with sexually dimorphic pruning of synapses and signaling mechanisms, in regions of the brain implicated in the development of depression. Hence, the onset of adolescent depression may be triggered by either insufficient overproduction or enhanced pruning in a sexual dysmorphic way (Andersen & Teicher, 2004). Moreover, according to Kerestes et al. (2014) an abnormal activation in the ventromedial and orbitofrontal frontal regions, the amygdala and the anterior cingulate in adolescents suffering from depression.

Moreover, Chen et al. (2010) noted hippocampus abnormalities evident in adolescent females with high familial risk, although none of the participants had ever experienced any depressive symptoms themselves. Moreover, in a study conducted by Bouma et al. (2008), the authors noted that daughters of parents with a history of depression displayed a blunted cortisol response, which daughters of non-depressed parents did not. Furthermore, Oldehinkel
and Bouma, (2011) also noted that granddaughters but not grandsons of individuals with depressive disorders exhibited elevated startle responses. Critically, due to lack of reach, no research concerning genetic vulnerability factors have been included yet without this critical component, any conclusion is a simplification. As genes, hormones, stress and the brain interact to cause psychopathological vulnerability. Hence, it is my conclusion that the maturation of the brain and specifically the PFC, may deem the adolescent emotional regulation system incapacitated to adequately deal with increasingly complex stimuli. Also, the hormonal surges may trigger previously silent genes, thus triggering the development of depressive symptoms in those genetically predisposed. Although all the different nodes have an important role to play, during the adolescent period genes and hormones that were previously silent may begin to play up, making psychopathology evident (Andersen & Teicher, 2008). Those not suffering from genetic predisposition to develop depression may need a more severe stressor, than those high in familial risk (Beck, 2008).

Moreover, an integrative view of depression is emphasized by the author, as arguably the brain, genes, hormones, the environment and the psychological makeup of the individual interact and combined these factors determine the mental health of the individual. Thus, with advances in research, the interplay between hormones, genes, stress and the brain will become increasingly delineated. Thus, future longitudinal studies with recurrent brain scans and a thorough focus on sex differences may generate a greater understanding of this complex disease that is depression and the related factors that entail its developmental journey.
Figure 1. The model depicts sex differences in depression vulnerability, thus emphasizing key contributing factors that might aid the development of the 2:1 ratio during adolescence. The figure is adapted from the ABC theory (Hyde et al., 2008).

8. Conclusion

To conclude, the 2:1 ratios emergence around mid-puberty can be contributed to the following vulnerability factors: early pubertal onset (Piccinelli & Wilkinson, 2000), females potential increased range of fluctuations in gonadal hormones (Oldehinkel & Bouma, 2011), increasing levels of gonadal hormones might lead to dysregulation of the HPA-axis in a sexually dimorphic way (Weiss et al., 1999), increased stress sensitivity and increased stress reactivity (Laviola & Marco, 2011), females increased number of overall stressors (Salk et al., 2016), increased sensitivity to interpersonal stress (Aube et al., 2000), females increased sensitivity to rejection stress (Stroud et al., 2002), females increased sensitivity to abnormal hippocampus maturation, accelerated amygdala growth and smaller nucleus accumbens (across time) (Whittle et al., 2014), hippocampus abnormalities due to high familial risk (Chen et al., 2010), females higher rates of ACEs (Piccinelli & Wilkinson, 2000), socio
cultural sex-roles and related aversive experiences (Piccinelli & Wilkinson, 2000), psychological attributes and coping skills that contribute to the vulnerability to depressive symptoms (Piccinelli & Wilkinson, 2000), puberty related physical changes that may possibly lead to increased rates of body dissatisfaction, restrained eating and eating disorders particularly in females (Bennetta et al., 2005; Girgus & Yang, 2015).

Furthermore, although research results currently available do suggest that there are significant sex differences evident within the adolescent brain, it is yet too early to draw any definite conclusion regarding possible behavioral implication due to the observed sex differences. In spite of that, research within the area has grown tremendously within the last two decades and further investigation emphasizing sex differences within the brain in relation to the depression symptoms and the 2:1 ratio, may yield continued understanding of key contributing factors and mechanisms (Hyde et al., 2008; Whittle et al., 2014). Moreover, as the included research becomes more widespread it may lead to improved therapy and medicinal treatment. Hence, I suggest that future research require upgraded DSM criteria that are improved with age and sex differences in mind to increase diagnostic validity (Blom et al., 2016), in addition to an truly integrative theory that emphasize neurodevelopmental sex differences and mechanisms potentially contributing to depression vulnerability and the 2:1 ratio, as well as biological influencers (hormonal and genetic), contextual factors (stressors) in addition to psychological attributes. Moreover, all these different vulnerability factors interact and in combination, they will be able to explain within-sex differences as well as individual differences (Hyde et al., 2008).
References


