

# HORMONAL AND DEVELOPMENTAL INFLUENCES ON ADOLESCENT SUICIDE: A SYSTEMATIC REVIEW

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## SUMMARY

**Background:** Teen suicide is a major public health problem. In the United States, it is the third cause of death among the 10-24 year olds. Adolescence involves numerous changes, whether physical, social, emotional or hormonal. At a neurobiological level, a teenager's nervous system is also affected and undergoes significant modifications.

**Subjects and methods:** We conducted a systematic review of electronic literature published between January 1990 and August 2014 via MEDLINE, PubMed and PsychINFO to list articles concerning the risk of teen depression and suicide risks in adolescents as well as those relating to the adolescent's neuro-anatomical brain and the effect that puberty has on it.

**Results and discussion:** When analyzing the various studies, it is clear that all support the idea that adolescence is a special period, both at neuroanatomical and biological levels. The risk of impulsiveness and depression is explained, anatomically, by a faster maturation of the limbic system, and biologically, by a higher sensitivity of the serotonergic system and to glucocorticoids, which themselves are influenced by the specific hormonal environment during this period. Moreover and above all, adolescence is a vulnerable time for many reasons: physical, hormonal, social, cognitive, and emotional changes, self-development, etc. We should not restrict it to structural neurological changes without taking into account the other factors or compartmentalize young people into a reductive model based on determinism.

**Conclusions:** Adolescence is a time of change, transformation, and adaptation. The hormonal events that occur during this period have significant effects on brain development, neuro-cerebral chemistry, adolescent behavior and risks of depression. It is important to try to prevent suicide and depression in adolescents considering its entirety and complexity but also by paying attention to neuro-biological factors even if, at present, many research projects are currently underway to develop an appropriate drug therapy strategy.

**Key words:** adolescent brain - neuro-biological factors – depression – cortisol - suicide

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## INTRODUCTION

Teen suicide is a major public health problem.

In the United States, it is the third cause of death among the 10-24 year olds (Centers for Disease Control and Prevention, 2010). A recent statistical study conducted in an American high school indicated that 15.8% of the population had seriously thought about attempting suicide over the past year; 12.8% had masterminded a plan and 7.8% had made one attempt (Center for Disease, 2007, Eaton et al. 2012). In the United Kingdom, between 2001 and 2010, 1,523 deaths were caused by suicide in subjects between 10 to 19 years old, which represents 2.25 per 1,00,000 inhabitants (3.14 males and 1.3 females) with an even higher rate for the 15 to 19 year olds (4.04 per 100,000) (Windfuhr et al. 2013). In France, a study conducted by the French national Inserm-CépiDc database reports that during 2007, in France, there were 520,535 deaths all etiologies included. The number of suicide deaths amounted to 10,127, which represents a rate of 16.4/100,000 inhabitants. These suicides concern 7,418 men (rate of 24.8/100,000) and 2,074 women (rate of 8.5/100,000). As for teenagers, in 2007, they represented a rate of 4.1/100,000 for the 15 to 19 year olds. This segment of the population involves twice as less suicides than the 20 to 24 year olds (Aouba 2011). It is important to note

that in the above paragraph, we are referring to the number of deaths caused by suicide, not suicide attempts. The suicide attempt rate is higher for young girls but the suicide death rate is higher among adolescent boys.

Adolescence involves numerous changes, whether physical, social, emotional or hormonal. At a neurobiological level, a teenager's nervous system is also affected and undergoes significant modifications. It is not just a simple transition, but a real transformation from a child's brain to an adult's. Numerous interactions occur between reproductive activity, the neural system regulating stress hormones produced as a result and the nervous system controlling the affects. During this period of reorganization, it has now been verified that an adolescent is more vulnerable from an emotional viewpoint. Many studies have examined the family social, demographic, and psychiatric factors of suicide risks and their prevention (Young 2007, Brunner 2007, Cox 2012, Fergusson 2003, Wilkinson 2011). Relatively few of them have investigated the biological risk of suicidal behavior during this period despite the fact that it is universally accepted that one of the most important risk factors for suicidal behavior in adolescents is depression. Other research work has focused on the specificity of the adolescent brain at a neuro-anatomical level and the influence of puberty on brain structures.

However, few studies have established a connection with the risk of depression or suicide at this age.

This article is based on a systematic literature review and aims to provide a better understanding of the suicidal risk in adolescents with a bio-neuro-anatomical approach. It supplements, in a common measure, a previous research study in which we established a connection between the impulsive behavior of adolescents and the neuro-anatomical development specific to this age. Our aim is not to disregard the other risk factors by advocating Neuroscience and Biology but to develop a different approach and provide a specific angle for studying suicide risks.

## METHOD

We conducted a systematic review of electronic literature published between January 1990 and August 2014 via MEDLINE, PubMed and PsychINFO to list articles concerning the risk of teen depression and suicide risks in adolescents as well as those relating to the adolescent's neuro-anatomical brain and the effect that puberty has on it. The following combinations were used: adolescents and suicide or depressive behavior, adolescent's brain and serotonin and cortisol. We excluded studies that were not written in English or French. In order to provide a better understanding of the subject, we have organized the results into two groups.

## RESULTS

### Neuro-cerebral development during adolescence

#### General

It is now universally accepted that brain plasticity continues beyond adolescence.

Thanks to innovative neuro-imaging techniques, various studies have contributed to the identification of certain specificities of anatomical brain development in adolescents. During this period, white matter (consisting of axons, myelin and glia) and grey matter (including cell bodies and a dendritic arborization) continue to undergo dynamic changes. The grey matter tends to decrease. This is essentially due to synaptic pruning which causes a volume reduction and not a decrease in cell numbers as such. This pruning process completes the dendritic arborization of neurons and specializes brain circuits (Holzer et al. 2011). The white substance, in turn, increases during this period and favors the transmission between different limbic structures, mainly the hippocampus and amygdala (major roles in the reward circuit and affects). This system matures relatively quickly in contrast to the prefrontal cortex (which plays a role in decision-making and emotional control) which is slow to myelinate. Therefore, there is a certain delay between the prefrontal cortex and the limbic system which generates, in teenagers, a period

involving a greater risk of impulsiveness. Moreover, it is important to note that during this period there is a difference in cerebral maturity between both sexes. This is explained, in major part, by the role played by sexual hormones during puberty but also by that of glucocorticoids.

#### **Puberty and effect of sexual hormones on the adolescent brain**

Puberty and adolescence are often used as synonyms and refer to the period of transition between childhood and adulthood. However, strictly speaking, both terms do not have the same meaning. Different definitions have been established for puberty. For understanding purposes, we will retain that of Buck Louis et al "Puberty is the period between childhood and adulthood characterized by the appearance of secondary sexual characteristics, an accelerating growth, behavioral changes and the acquisition of the ability to reproduce". Different approaches to establish the onset of puberty and its progression have been developed by using Tanner stages, the age of menarche in girls or the beginning of spermatozoid production in boys, the use of biochemical markers, etc. As part of our review, we will particularly examine hormonal influence on the brain. These hormonal changes start with the activation of the hypothalamic-pituitary gonadal (HPG) axis. The hypothalamus begins to secrete GnRH, which stimulates the pituitary gland. This causes the release of LH and FSH in the blood. Both of these hormones act jointly to develop spermatogenesis in boys and oogenesis in girls, as well as to stimulate sexual organs in order to produce testosterone and estrogen. The increase in the levels of both of these hormones causes secondary sexual characteristics in both sexes (Sisk 2005).

But what is the role of sexual hormones at a cerebral level? This role is particularly well explained by Rhoshel et al's study on the differences of the adolescent brain in both sexes. In this study, the author explains that the volume of a male adolescent is greater than that of a female adolescent, but that the peak volume is reached at a later stage in girls. Furthermore, it is shown that the GM/WM ratio is higher in women. Therefore, there appears to be a significant connection between brain development and hormonal influence during that period (Ladouceur 2012). Estrogen seems to influence the amount of dendritic branching and synaptogenesis and to delay synaptic pruning, whereas testosterone appears to affect myelination (De Bellis 2001). Other studies have documented this sexual dysmorphism in various regions including the hypothalamus, amygdala, hippocampus, striatum, and cerebellum, as well as in different regions of the cerebral cortex such as the frontal cortex, sensorimotor cortex, and posterior parietal cortex (Giedd 1996, Murphy 1996, Goldstein 2001, Tiemeier 2010). Our representation of the role of sexual hormones in these areas is still incomplete but recent studies using techniques such as immunohistochemistry and technical hybridization have made it

possible to identify the cellular locations of steroid receptors. It is interesting to note that the regions showing the greatest difference between both sexes are the basal ganglia and limbic structures. The hippocampus appears to possess a higher rate of estrogen receptors. However, the amygdala would have a greater amount of androgen receptors (Clark 1988, Holzer 2011). These above-mentioned structures are therefore sensitive to sexual hormones.

### ***Effect of cortisol on the adolescent brain***

During puberty, the hypothalamic pituitary axis also has another function: the production of glucocorticoids through the stimulation of the cortex of the adrenal gland (HPA axis or hypothalamic-pituitary-adrenal axis). This is performed via the CRH (corticotrophin-releasing hormone) from the cells of the paraventricular hypothalamus and the ACTH (adrenocorticotropin-releasing hormone), secreted by the basophil cells of the anterior lobe of the pituitary. A negative feedback is exerted on the different structures by cortisol itself. It is recalled that, in adults, the role of this axis is to fight external challenges. The body's response to fight stress is to increase the level of glucocorticoids. Many studies have examined the understanding of this process during adulthood or childhood but not during adolescence. The effect of sexual hormones on this axis is also important. During adulthood, basal cortisol levels are higher in women. Several explanations exist: estradiol that increases the corticosterone levels while testosterone tends to decrease them, androgens that reduce the levels of globulin (CBG: corticosteroid binding) in both sexes while estradiol increases the levels in men alone. Only cortisol not bound to CBG is active in the plasma (McCormick 2002, Nock 2000, Paulmyer-Lacroix 1996, Viau 2004).

In adolescents, there appears to be a greater sensitivity of the axis to stress factors and increased basic cortisol levels due to an immaturity of the negative feedback of cortisol on ACTH and CRH (other genetic factors also appear to be involved (McCormick 2007)). The hyperactivity of the axis and high cortisol levels appear to be related to depressive symptoms. The glucocorticosteroid receptors are located in many cerebral locations and it is interesting to note that their density is higher on the amygdala and hippocampus. A study performed on patients suffering from congenital adrenal hyperplasia established that the volume of the amygdala had significantly decreased in men and women with this disease (Merke 2002, Giedd 2006). The hormones responsible for this decrease in size were excess androgen, estrogen or progestin or excess exogenous glucocorticoids or this reduction was caused by a deficiency of the endogenous glucocorticoids or a combination of all of these phenomena. A study concerning the development of depressive symptoms in these patients, in particular, should be considered. In depressive teenagers, there is an insufficient number of glucocorticoid receptors including on the pituitary and amygdala.

### **Adolescence and depression**

Before puberty, there is a similar depression rate between boys and girls (Angold 1998). With the onset of puberty, the rate tends to increase in girls. Most studies show that the difference becomes significant around 13-14 years old (McGee 1992, Nolen-Hoeksema 1994, Hankin 1998, Twenge 2002, Wade 2002, Kessler 2005). Different explanations can be given: higher rates of exposure to trauma in women, higher sensitivity or attachment, etc. as well as a difference in the response of the hypothalamic-pituitary axis, which appears to be increased in women but decreased in men probably due to the increase in testosterone levels (McCormick 2007). A recent study conducted by Toffoletto et al. explains that estrogen and progestin, in addition to their influence on the brain structures themselves (see above para), have a major effect on moods and cognition through their influence on neurotransmitters: especially on serotonergic systems (5HT) and dopamine (DA) and through the interaction occurring between dopamine, estradiol and TPH (allopregnanolone) (Gasbarri 2012, Weiss 2014, Shanmugan 2014, Zheng 2009). Genetic neuro-imaging studies have also reported a complex but significant interaction between BDNF (Brain-Derived Neurotrophic Factor), the HTT serotonin 5 transporter and ovarian hormones in the prefrontal regions. This could also explain the mood swings occurring during menstrual cycles in women.

Another biological hypothesis to consider is the role played by cortisol during adolescence and in depressed patients. Such as expressed above, adolescence is a period of vulnerability and significant stress. The hyperactivity of the HPA axis (see above para) generates high cortisol levels, which appear to affect certain structures, including the limbic system, as well as neurogenesis. This could lead to the development of depressive symptoms (Gregus 2005). Another identified factor is the activation of the HPA and the influence of cortisol on brain serotonin levels. A high cortisol level causes a reduction of circulating serotonin levels via several mechanisms. Firstly, a reduction of its action occurs at the level of 5HT1A and 5HT1B receptors in the hippocampus and at the level of 5HT2 receptors in the cortex (Lopez 1997). Secondly, the action of glucocorticoid receptors located on the serotonergic projections from the raphe nuclei in the hippocampus (Sher 2007) is also involved.

### **DISCUSSION**

When analyzing the various studies, it is clear that all support the idea that adolescence is a special period, both at neuroanatomical and biological levels. The risk of impulsiveness and depression is explained, anatomically, by a faster maturation of the limbic system, and biologically, by a higher sensitivity of the serotonergic system and to glucocorticoids, which themselves are influenced by the specific hormonal environment during this period. As a result, would a teenager be more at risk of attempting suicide due to these factors? Most likely.

However, this is a topic that is to be addressed carefully. Even if a serotonergic change occurs at this time, it is itself influenced by dopaminergic, gabaergic, glutamatergic and noradrenergic impregnation but also by the hormonal environment, inflammatory processes and the environment.

Moreover and above all, adolescence is a vulnerable time for many reasons: physical, hormonal, social, cognitive, and emotional changes, self-development, etc. We should not restrict it to structural neurological changes without taking into account the other factors or compartmentalize young people into a reductive model based on determinism. Due to the rapid developments achieved in recent years in the field of functional magnetic resonance imaging and immunohistochemistry, the risk of such an approach exists and it would be dangerous to believe that it is possible to analyze or understand human beings by mapping the human brain or assimilating emotions to neurotransmitter levels. This could cause drifting at a medical level, but also at a societal or even political level. Let's take the example of a young fifteen year old who has committed an offense under the influence of drugs. How can we care for and manage him, both from medical and legal viewpoints if he is sitting on the dock with no possibility of change? If, whatever he does or undertakes, the result is only determined neuro-biologically, anatomically or even, by extrapolation, genetically? What would happen if the possibility of change based on experience, questioning or thinking was not taken into account? The only solution, the only possible therapy would be drug-based and the human brain would be reduced to an organ in its simplest form without its human and subjective dimension.

## CONCLUSION

Adolescence is a time of change, transformation, and adaptation. Whether physical, social, environmental, anatomical or biological. These changes make it a vulnerable period. The hormonal events that occur during this period have significant effects on brain development, neuro-cerebral chemistry, adolescent behavior and risks of depression. It is important to try to prevent suicide and depression in adolescents considering its entirety and complexity but also by paying attention to neuro-biological factors even if, at present, many research projects are currently underway to develop an appropriate drug therapy strategy.

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