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Stress, hormones and the adolescent brain

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Executive Summary

- Acute stressors activate the autonomic nervous system and the hypothalamic–pituitary adrenal (HPA) axis
- The onset of puberty increases the risk of stress-related psychopathology, and discernible sex differences in psychopathology can be observed during adolescence.
- There are reciprocal interactions between the HPA and the Hypothalamic–pituitary–gonadal (HPG) axis in adolescence). For example, gonadal hormones such as estradiol, progesterone and testosterone influence HPA axis function by sensitizing or desensitizing the individual to certain types of stressors.
- Stress modulates a number of cognitive functions during adolescence, including social status, reward processing and learning.
- Neuroimaging findings reveal changes in the brain systems underlying these cognitive functions in adolescents compared to adults.
- A recent hypothesis is that acutely stressful events, characterized by their unpredictability, elicit a cumulative teaching signal for the brain which promotes rapid learning of the ongoing events.
- This hypothesis may explain enhanced memory for stressful events, stress-related mental disorders such as post-traumatic disorder and the fact that a release of dopamine is commonly observed during stressful episodes.
- State anxiety and trait anxiety are associated with changes in brain activity in partially specific brain systems.
- Education and intervention programs, aimed at moderating risk-taking behavior in adolescence, should benefit from a better understanding of the neural mechanisms underlying reward processing and risky decision-making.
- In conclusion, stress interacts with multiple hormonal systems during adolescence and modulates brain systems underlying cognitive, motivational, learning and emotional functions.

Introduction: stress and the adolescent brain

Adolescence is a sensitive period for social stress. With the onset of puberty stress-reactivity abruptly increases, as does the risk for development of psychopathology, while the recovery from chronic social stress is compromised. This suggests a link between stress physiology and sexual maturation during adolescence (Fuhrmann et al., 2015). The neuroendocrine responses to social stress and their consequences for the adolescent brain have started to be characterized in the past few years.

Neuroendocrine interactions in the stress response

Acute stressors activate the autonomic nervous system and the hypothalamic–pituitary adrenal (HPA) axis, resulting in biological changes such as cortisol release, and alterations in neural activity. The cascade of the neuroendocrine stress response by the HPA axis starts at the hypothalamus and ends in the adrenal gland, from which cortisol is secreted during acute stress (**Figure 1, left**). Cortisol has been implicated in physiological responses to stressors (e.g., providing energy resources to engage fight-or-flight mechanisms), and can be effectively down-regulated through various feedback-loops with upstream

structures of the HPA axis after stressor-offset. If cortisol remains chronically elevated, this can have detrimental effects on individual well-being and promotes psychopathology including depression and anxiety disorders (Lupien et al., 2009). Other adrenal hormones, including progesterone and Allopregnanolone (ALLO), are also secreted during acute stress. They may protect against the negative effects of cortisol by acutely dampening the hyperactive HPA axis through various routes (Wirth, 2010a). Interestingly, evidence from rodents suggests that the stress protective anxiolytic function of ALLO, normally observed in adults, appears to be reversed during adolescence. During adolescence, ALLO may act on a specific population of extra-synaptic Gamma-aminobutyric acid A receptors (GABA-A) in the brain, through which GABA-mediated inhibition is paradoxically reduced. Thus ALLO leads to an exacerbation of the acute stress response in adolescents rendering the brain more vulnerable to stressors (Smith, 2013).

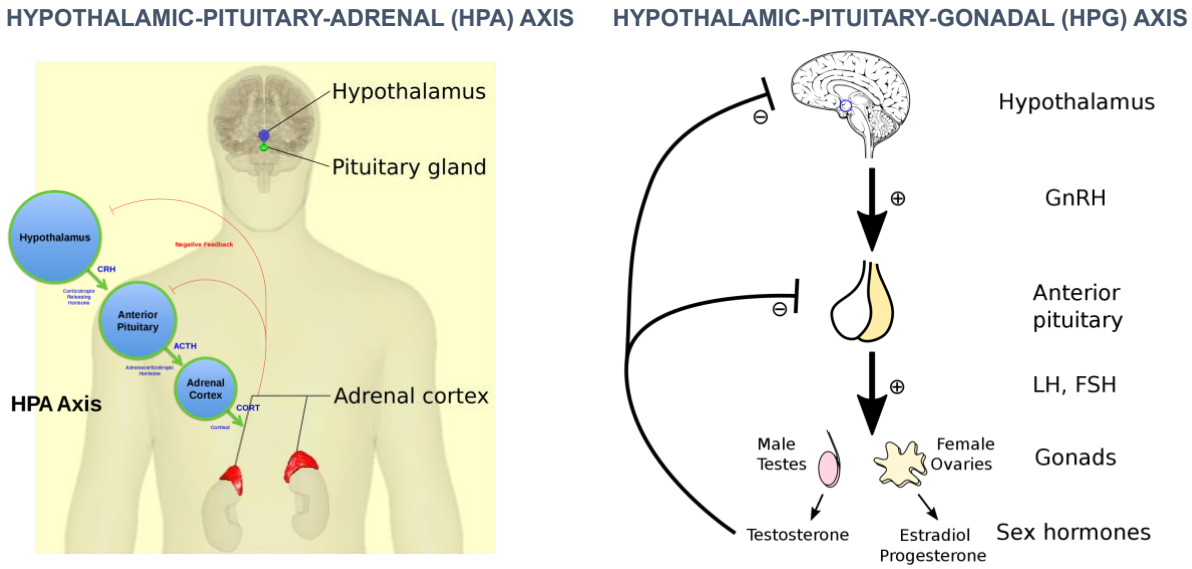

Figure 1. Left. The neuroendocrine stress response engages the hypothalamic–pituitary adrenal (HPA) axis starting at the hypothalamus and ending in the adrenal gland, from which cortisol is secreted during acute stress. Right. The Hypothalamic–pituitary–gonadal (HPG) includes the hypothalamus, pituitary gland and gonadal glands. It plays a key role in the development and regulation of the reproductive and immune systems.

The onset of puberty increases the risk for stress-related psychopathology, and discernible sex differences in psychopathology can be observed for the first time (Stroud et al., 2002). Puberty also marks the abrupt increase of stress-sensitivity in the adolescent brain (Spear, 2000). In late childhood, the HPA and the Hypothalamic–pituitary–gonadal (HPG) axes both increase the production of steroid hormones to initiate sexual maturation (Marceau, Shirtcliff, et al., 2014) (**Figure 1, right**). Since the interaction between the HPG and HPA axes is reciprocal (Marceau, Ruttle, et al., 2014; Panagiotakopoulos & Neigh, 2014), gonadal hormones such as estradiol, progesterone and testosterone, whose concentrations differ between sexually maturing males and females, influence HPA axis function by sensitizing or desensitizing the individual to certain types of stressors. Studies of rodents suggest that estrogens can amplify the adult stress response (Burgess & Handa, 1992), while testosterone may reduce the responsiveness of the adult HPA axis (Terburg et al., 2009). In humans, an interaction between the HPA and HPG axes has also been documented, but findings are less consistent. On the one hand, there is a sex difference in the salivary cortisol response to the Trier Social Stress Task (TSST), a classical task activating the HPA axis after a social evaluative situation in front of a panel of judges, along with a videocamera and audio recorder. Indeed, adult men exhibit an enhanced response compared to women (Liu et al., 2017). On the other hand, studies

that took into account hormonal changes across the menstrual cycle, or hormonal contraception in women, found that estradiol and synthetic ethinylestradiol were both associated with a reduced cortisol response to the TSST (Kirschbaum et al., 1999). This was supposedly caused by the boosting effect of these hormones on corticosteroid binding globulin, which reduce the availability of bioactive cortisol (Pruessner, 2018). Conversely, during a state of enhanced gonadal progesterone and ALLO, i.e., in the luteal phase, the cortisol stress-response to the TSST was more similar to that in men (Kirschbaum et al., 1999).

Progesterone, ALLO, and testosterone levels parallel the acute stress-induced increase in cortisol, suggesting an adrenal rather than gonadal source of release (Childs et al., 2010; Deuter et al., 2021; Lennartsson et al., 2012; Wirth, 2010b; Wirth et al., 2007)(Schoofs & Wolf, 2011). Higher testosterone may thus support the adaptation to the social challenge inherent to most social stressors, particularly in men, and might compensate for the negative effects of stress (Lennartsson et al., 2012; Mehta & Prasad, 2015; Van Anders et al., 2011). However, it could also indicate heightened stress vulnerability (Knight et al., 2017), especially in contexts in which social status needs to be asserted (Knight & Mehta, 2016). Progesterone and ALLO may have an anxiolytic function in adults, and might promote affiliation and bonding responses during stress coping (Wirth, 2010b). In human adolescents, the nature of the hormonal interactions during the acute stress response remains undetermined and given the puberty-related increase in stress pathology, an investigation of the HPG-HPA axes interaction during social stress in adolescents is overdue.

Social cognition and the stress response during adolescence

Adolescence is a period of increasing self-sufficiency and independence (Kilford et al., 2016) during which adolescents try to attain and consolidate social status within the peer group. Thus, it is not surprising that the salience of social status peaks during adolescence, and dominance relationships between peers become increasingly important (Espelage & Holt, 2015). Dominant status within a given peer group (e.g., school class) can be acquired through direct or indirect acts of aggression, or by affiliative prosocial behaviors, that are equally weighed as high status attributes within adolescent peer groups (Koski et al., 2015; Pouwels et al., 2016). It is likely that adolescents are equipped with brain mechanisms and hormonal responses that allow them to identify markers of dominance, e.g., to keep track of evolving social hierarchies, and to be aware of their own social status within a given social group. In the face of social challenges like the TSST, that put social status at risk, neuroendocrine responses are likely to be engaged, that not only mobilize energy resources, (such as increased cortisol), but that could also facilitate competitive performance, (such as increased testosterone) (Turan et al., 2015). However, as in adults, inter-individual differences in personality characteristics (dominant vs. anxious), and individual stress levels might influence adolescent status sensitivity. The increased salience of social interactions and the importance of status acquisition during adolescence suggest an even stronger influence of stress and inter-individual differences on neural processing than previously observed in adults.

During adolescence the influence of affective and cognitive brain systems on behavior is assumed to be unbalanced (Kilford et al., 2016). Affective regions such as the amygdala and the anterior cingulate cortex (ACC) show an increased sensitivity to social information, while prefrontal regions such as the rostromedial prefrontal cortex (rmPFC), that are also implicated in higher-order stress regulatory processes and inhibitory control, may still be immature (Crone & Dahl, 2012; Koski et al., 2015). This could be one reason why adolescents are particularly sensitive to social stressors.

In adolescents, this sensitivity was found to be reflected by a heightened response of the anterior cingulate cortex to peer feedback, such as peer rejection, and an already marginalized social status increased the risk for depressive symptoms (Foulkes & Blakemore, 2018; Gillies & McArthur, 2010; Koski et al., 2015; Rudolph et al., 2016; Will et al., 2016). Part of the same circuit is also involved in processing information related to social status in the adult brain, including social hierarchy learning (Ligneul et al.,

2016). Furthermore, a modulation of this circuit by gonadal hormones (e.g., testosterone) has been demonstrated (Mehta & Beer, 2010). Together, these data suggest that adolescents are expected to show increased sensitivity to status-relevant information, either because of hyperactive affective centers (e.g., amygdala, ACC), or underactive inhibitory prefrontal regions (such as the rmPFC), or a combination of both (Koski et al., 2015).

Reward processing in adolescents

Changes in BOLD response have been observed when comparing adolescents to healthy adults in a number of domains, such as reward processing and executive functions. For example, adolescent reward processing was increased in limbic, frontolimbic, and striatal regions compared with adults (Ernst et al., 2005; Silverman et al., 2015; van Duijvenvoorde et al., 2016; Van Leijenhorst et al., 2010) (**Figure 2**). In contrast, adults engage more executive control regions of the frontal and parietal lobes relative to adolescents. These findings support hypothesized elevations in motivated activity during adolescence and reduced cognitive control mechanisms relative to adults. Compared to adults, adolescents were reported to exhibit increased activity of the striatal and limbic system to large rewards, which suggests greater sensitivity of these regions to larger rewards, with a peak reward response occurring around the age of 14–15 (Casey et al., 2008; Doremus-Fitzwater et al., 2010). Neurodevelopmental studies report a surge in sensation seeking during adolescence that is accompanied by higher activation of the reward system during adolescence (Steinberg & Chein, 2015), and which may lead to increases in peer influence and risky behavior (Steinberg et al., 2008). Recent approaches have linked these changes in motivated behavior to long-lasting neurodevelopmental changes across adolescence. This heightened reward-sensitivity in adolescents may be related to two behavioral domains: risk taking and cognitive control. When confronted by novel situations that bring the potential for positive reinforcement (Silverman et al., 2015), adolescents may be motivationally biased toward reward pursuit because of heightened sensitivity to incentive-based stimuli, perhaps to the point of taking more risks and reducing cognitive control/inhibitory processes (Van Leijenhorst et al., 2010).

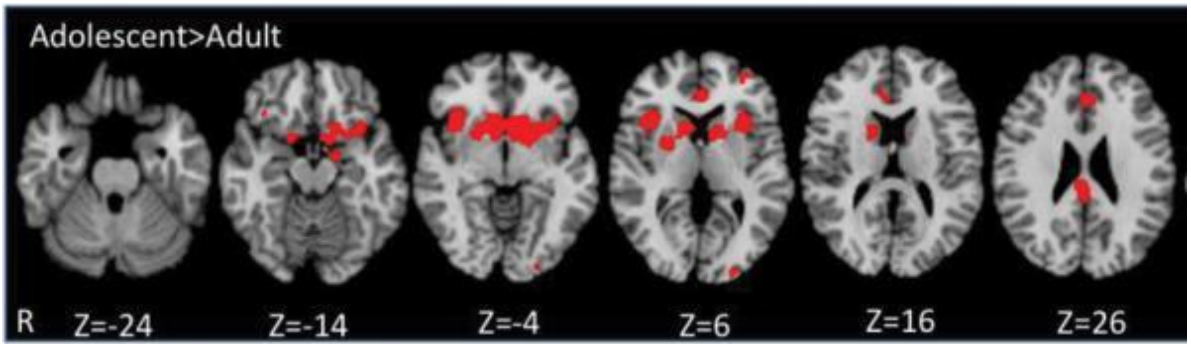

Figure 2. Brain areas showing increased likelihood for activation in adolescents relative to adults. Cluster locations include subcortical regions such as the ventral and dorsal striatum and the amygdala as well as the anterior and posterior cingulate cortex and the orbital frontal cortex. Reproduced from Silverman et al., 2015.

Activation of these reward regions across adolescence may depend on interactions with late-maturing brain regions such as the lateral PFC and parietal cortex. These regions have frequently been implicated in cognitive control functions (e.g., response inhibition, relational reasoning, working memory, and learning). Additionally, co-activations are regularly observed between reward-related regions and brain regions important for perspective taking, mentalizing and social behaviors, including the medial PFC and the temporal-parietal junction. Furthermore, social context plays a great role in adolescent reward-sensitivity across different social domains including peer presence, peer influence, and vicarious rewards (van Duijvenvoorde et al., 2016). Recent studies have examined the neural correlates of these social influences on reward-related brain activity in adolescence.

Stress, Reinforcement learning and dopamine

A large number of studies in animals indicate that testosterone and estrogen modulate dopamine signaling (Becker & Chartoff, 2019; Wood, 2004), and may further regulate some of the developmental changes in dopamine systems across adolescence (Sinclair et al., 2014). The increase in testosterone during male adolescents could therefore affect Reinforcement Learning (RL) (see brief on this topic by same Dreher), as well as the processing of social rewards. Increased progesterone is also expected to impact dopaminergic transmission and RL, as suggested by evidence from both rodents and humans (Diekhof et al., 2020; Diekhof & Ratnayake, 2016; Dluzen & Ramirez, 1984). For these reasons, an interaction between the brain systems engaged in (non-social) RL and adolescent hormones may also be assumed, particularly under stress (Bell & Sisk, 2013; Purves-Tyson et al., 2014; Sinclair et al., 2014).

In addition to gonadal steroid hormones influences on dopaminergic function, acute psychological stress appears to enhance dopaminergic transmission, not only in adults but also in the adolescent brain (Sinclair et al., 2014; Tottenham & Galván, 2016; Vaessen et al., 2015). Reward sensitivity peaks around 15 years of age, supposedly as a consequence of a hyperactive dopamine system (Galván, 2013). One may thus expect that stress further magnifies dopaminergic transmission in the hyperactive adolescent dopamine system (Datta & Arnsten, 2019), which may also affect RL. One interesting hypothesis is that stress, in terms of cumulative prediction errors (PEs), promotes rapid learning of events (Kalbe et al., 2020; Trapp et al., 2018; Zerbes et al., 2020). A PE represents the mismatch between prediction and real sensory input and can therefore signal false beliefs about the structure of the world. This hypothesis may explain enhanced memory for stressful events as well as stress-related mental disorders such as post-traumatic disorder. The traditional view is that superior memory for stressful events would be due to increased arousal and the operation of adrenaline, noradrenaline, and glucocorticoids (Joëls et al., 2011). These two hypotheses are compatible with each other. However, the new hypothesis is that acutely stressful events, characterized by their unpredictability, elicit a PE that acts as a teaching signal for the brain and promotes rapid learning of the ongoing events. This hypothesis thus proposes a computational account of stressful events and also accounts for the fact that a release of dopamine is commonly observed during stressful episodes (Butts et al., 2011). The timescale of the rapid PE operates within milliseconds while stress operates over a longer period. This hypothesis proposes that stress can be viewed as an accumulation of PE: an average of PEs across a period of time would become an approximate measure of uncertainty. The link between dopamine release in response to stress and striatal BOLD response observed with reward processing can be made with a recent study combining optogenetics and fMRI in rats. This study showed that dopamine neuron stimulation is directly related to striatal BOLD activity (Ferenczi et al., 2016).

Brain systems engaged in Risk taking in adolescence:

A substantial body of evidence indicates an increase of risk-taking behavior in both real-life and experimental settings during adolescence (Boyer, 2006; Steinberg, 2004). Activation in reward areas such

as the ventral striatum has been related to real-life risk taking behavior, eg. risky sexual behavior, illicit drug use and binge drinking (Bjork & Pardini, 2015). There are at least two views on the neural bases of adolescent risk-taking behavior. According to one view, based on consideration of maturation-related changes of the adolescent brain, there is a developmental imbalance between slowly maturing regulatory processes such as inhibitory control, that involves the inferior frontal and anterior cingulate cortices, and faster maturing reward-motivational processes, including the ventral striatum and amygdala. This imbalance would underly the suboptimal decision-making in adolescence (Casey et al., 2008; Jentsch & Taylor, 1999; Somerville et al., 2010). The second view considers that adolescents are not more risk seeking than adults when making decisions between a safe option and a risky option, with known probability of each possible outcome. In contrast, adolescents show increased willingness to accept ambiguous conditions (i.e. situations in which the likelihood of winning and losing is unknown) (van den Bos & Hertwig, 2017). Relative to children and adults, adolescents were more accepting of uncertainty, as indicated by shorter pre-decisional search (van den Bos & Hertwig, 2017)). This tolerance of the unknown was associated with motivational, but not cognitive, factors. These findings offer novel insights into the psychology of adolescent risk taking. Thus, it is not risk seeking but ambiguity (i.e. not knowing the reward probabilities) and/or uncertainty which seem dysfunctional in adolescence. One study showed a linear decrease in ambiguity tolerance with age between 10–25 years (Blankenstein et al., 2016), another study identified a quadratic trend peaking at 15–16 years (van den Bos & Hertwig, 2017). Thus, adolescents' brain responses to risk may be better captured under conditions when the probabilities of good and bad outcomes are not explicit, which is typical for most real-life situations with potentially adverse consequences (drug use, reckless driving, unprotected sex, etc.).

Importantly, risky behaviors with known and unknown probabilities seem to be driven by different neural mechanisms in adults. For example, a classic fMRI study reported that activation from the lateral prefrontal cortex was predicted by ambiguity preference while activation of the posterior parietal cortex was predicted by risk preference (Hsu et al., 2005; Huettel et al., 2006) (Huettel et al., 2006). Another fMRI study reported that the level of ambiguity in choices correlates positively with activation in the amygdala and orbitofrontal cortex, and negatively with a striatal system (Here you Need a reference). In adolescents, the tendency to engage in risk taking under ambiguity (unknown probabilities) has been associated with reduced dorsomedial prefrontal cortex (DMPFC) and insula activation, while risky gambles with known probabilities were associated with ventral striatal activation and may be triggered by reward valuation (Blankenstein et al., 2016).

State versus trait anxiety in adolescents

One important distinction is between trait and state anxiety. Trait anxiety is a fixed part of our personality. A higher level of trait anxiety means that one individual is more likely to feel threatened by specific situations than someone with lower levels of trait anxiety. In contrast, state anxiety refers to the specific state in which one is at a given moment. State anxiety is triggered by situations of stress such as potential threat or other frightening situations, and usually involves a mix of mental (feeling worry, difficulty concentrating, irritability) and physical symptoms. Half of all lifetime cases of mental illness emerge before individuals turn 14 years old, and three quarters occur before age 24 (Kessler et al., 2005). In particular, nearly one third of adolescents have an anxiety disorder, and these adolescents are significantly more likely to present psychiatric conditions in adulthood (Doering et al., 2019). In addition to characterizing how the adolescent brain and cascade of hormones responds in reaction to acute stress in adolescence, a large number of neurobiological studies have investigated inter-individual variability due to differences in trait anxiety. One finding is that trait anxiety may be associated with either increased or decreased hippocampal and ventral striatum activation and decreased putamen activity (Corr et al., 2021; Lago et al., 2017).

Conclusion

Education and intervention programs, aimed at moderating risk-taking behavior in adolescence, should benefit from a better understanding of the neural mechanisms underlying reward processing, risky decision-making and decision making under unknown probabilities (ambiguity). Recent neuroscience models attribute sex differences in risk preferences to divergent and permanent reorganization of brain circuits during adolescence in boys and girls, partially driven by differential effects of sex hormones in the brain (Vigil et al., 2016). Given that sex hormones influence development of adolescent neural circuitry, affect emotions and interact with stress, future experimental research should aim to explain whether and how sex differences in risk-taking behavior, that emerge during adolescence, are reflected in divergent patterns of brain activity.

One interesting new direction for policy interventions emerges from the findings that adolescents may be more sensitive to ambiguity (unknown probabilities). These findings suggest that providing information on relevant outcomes and their probabilities would probably not be a successful prevention strategy (van den Bos & Hertwig, 2017). Instead, it may be more successful to afford adolescents (virtual) experience, including the experience of rare, consequential events.

Finally, further progress in cognitive neuroscience research in adolescents may benefit by not restricting calendar age as the level of development. Brain changes observed during adolescence now need to be related not simply to chronological age, but to biological maturity based on pubertal development and social maturity (Braams et al., 2015).

References

Becker, J. B., & Chartoff, E. (2019). Sex differences in neural mechanisms mediating reward and addiction. *Neuropsychopharmacology*, *44*(1), 166–183. https://doi.org/10.1038/s41386-018-0125-6

Bell, M. R., & Sisk, C. L. (2013). Dopamine mediates testosterone-induced social reward in male syrian hamsters. *Endocrinology*, *154*(3), 1225–1234. https://doi.org/10.1210/en.2012-2042

Bjork, J. M., & Pardini, D. A. (2015). Who are those "risk-taking adolescents"? Individual differences in developmental neuroimaging research. *Developmental Cognitive Neuroscience*, *11*, 56–64. https://doi.org/10.1016/j.dcn.2014.07.008

Blankenstein, N. E., Crone, E. A., van den Bos, W., & van Duijvenvoorde, A. C. K. (2016). Dealing With Uncertainty: Testing Risk- and Ambiguity-Attitude Across Adolescence. *Developmental Neuropsychology*, *41*(1–2), 77–92. https://doi.org/10.1080/87565641.2016.1158265

Boyer, T. W. (2006). The development of risk-taking: A multi-perspective review. *Developmental Review*, *26*(3), 291–345. https://doi.org/10.1016/j.dr.2006.05.002

Braams, B. R., Duijvenvoorde, A. C. K. van, Peper, J. S., & Crone, E. A. (2015). Longitudinal Changes in Adolescent Risk-Taking: A Comprehensive Study of Neural Responses to Rewards, Pubertal Development, and Risk-Taking Behavior. *Journal of Neuroscience*, *35*(18), 7226–7238. https://doi.org/10.1523/JNEUROSCI.4764-14.2015

Burgess, L. H., & Handa, R. J. (1992). Chronic estrogen-induced alterations in adrenocorticotropin and corticosterone secretion, and glucocorticoid receptor-mediated functions in female rats. *Endocrinology*, *131*(3), 1261–1269. https://doi.org/10.1210/endo.131.3.1324155

Butts, K. A., Weinberg, J., Young, A. H., & Phillips, A. G. (2011). Glucocorticoid receptors in the prefrontal cortex regulate stress-evoked dopamine efflux and aspects of executive function. *Proceedings of*

the National Academy of Sciences, *108*(45), 18459–18464. https://doi.org/10.1073/pnas.1111746108

Casey, B. J., Getz, S., & Galvan, A. (2008). The adolescent brain. *Developmental Review*, *28*(1), 62–77. https://doi.org/10.1016/j.dr.2007.08.003

Childs, E., Dlugos, A., & Wit, H. D. E. (2010). Cardiovascular, hormonal, and emotional responses to the TSST in relation to sex and menstrual cycle phase. *Psychophysiology*, *47*(3), 550–559. https://doi.org/10.1111/j.1469-8986.2009.00961.x.Cardiovascular

Corr, R., Pelletier-Baldelli, A., Glier, S., Bizzell, J., Campbell, A., & Belger, A. (2021). Neural mechanisms of acute stress and trait anxiety in adolescents. *NeuroImage: Clinical*, *29*, 102543. https://doi.org/10.1016/j.nicl.2020.102543

Crone, E. A., & Dahl, R. E. (2012). Understanding adolescence as a period of social-affective engagement and goal flexibility. *Nature Reviews Neuroscience*, *13*(9), 636–650. https://doi.org/10.1038/nrn3313

Datta, D., & Arnsten, A. F. T. (2019). Loss of prefrontal cortical higher cognition with uncontrollable stress: Molecular mechanisms, changes with age, and relevance to treatment. *Brain Sciences*, *9*(5), 1–16. https://doi.org/10.3390/brainsci9050113

Deuter, C. E., Duesenberg, M., Hellmann-Regen, J., Metz, S., Roepke, S., Wolf, O. T., Otte, C., & Wingenfeld, K. (2021). Psychosocial stress increases testosterone in patients with borderline personality disorder, post-traumatic stress disorder and healthy participants. *Borderline Personality Disorder and Emotion Dysregulation*, *8*(1). https://doi.org/10.1186/s40479-021-00145-x

Diekhof, E. K., Korf, S., Ott, F., Schädlich, C., & Holtfrerich, S. K. C. (2020). Avoidance Learning Across the Menstrual Cycle: A Conceptual Replication. *Frontiers in Endocrinology*, *11*. https://doi.org/10.3389/fendo.2020.00231

Diekhof, E. K., & Ratnayake, M. (2016). Menstrual cycle phase modulates reward sensitivity and performance monitoring in young women: Preliminary fMRI evidence. *Neuropsychologia*, *84*, 70–80. https://doi.org/10.1016/j.neuropsychologia.2015.10.016

Dluzen, D. E., & Ramirez, V. D. (1984). Bimodal effect of progesterone on in vitro dopamine function of the rat corpus striatum. *Neuroendocrinology*, *39*(2), 149–155. https://doi.org/10.1159/000123971

Doering, S., Lichtenstein, P., Gillberg, C., Boomsma, D. I., van Beijsterveldt, T. C. E. M., Ligthart, L., Willemsen, G., de Geus, E., Middeldorp, C. M., Bartels, M., Kuja-Halkola, R., Lundström, S., & NTR. (2019). Anxiety at age 15 predicts psychiatric diagnoses and suicidal ideation in late adolescence and young adulthood: Results from two longitudinal studies. *BMC Psychiatry*, *19*(1), 363. https://doi.org/10.1186/s12888-019-2349-3

Doremus-Fitzwater, T. L., Varlinskaya, E. I., & Spear, L. P. (2010). Motivational systems in adolescence: Possible implications for age differences in substance abuse and other risk-taking behaviors. *Brain and Cognition*, *72*(1), 114–123. https://doi.org/10.1016/j.bandc.2009.08.008

Ernst, M., Nelson, E. E., Jazbec, S., McClure, E. B., Monk, C. S., Leibenluft, E., Blair, J., & Pine, D. S. (2005). Amygdala and nucleus accumbens in responses to receipt and omission of gains in adults and adolescents. *NeuroImage*, *25*(4), 1279–1291. https://doi.org/10.1016/j.neuroimage.2004.12.038

Espelage, D. L., & Holt, M. (2015). Psychosocial Correlates in Bullying and Victimization Psychosocial Correlates in Bullying and Victimization: The Relationship Between Depression , Anxiety , and Bully / Victim Status. *Journal of Emotional Abuse*, *6798*(December), 37–41. https://doi.org/10.1300/J135v02n02

Ferenczi, E. A., Zalocusky, K. A., Liston, C., Grosenick, L., Warden, M. R., Amatya, D., Katovich, K., Mehta, H., Patenaude, B., Ramakrishnan, C., Kalanithi, P., Etkin, A., Knutson, B., Glover, G. H., &

Deisseroth, K. (2016). Prefrontal cortical regulation of brainwide circuit dynamics and reward-related behavior. *Science*, *351*(6268), aac9698. https://doi.org/10.1126/science.aac9698

Foulkes, L., & Blakemore, S. J. (2018). Studying individual differences in human adolescent brain development. *Nature Neuroscience*, *21*(3), 315–323. https://doi.org/10.1038/s41593-018-0078-4

Fuhrmann, D., Knoll, L. J., & Blakemore, S.-J. (2015). Adolescence as a Sensitive Period of Brain Development. *Trends in Cognitive Sciences*, *19*(10), 558–566. https://doi.org/10.1016/j.tics.2015.07.008

Galván, A. (2013). The Teenage Brain: Sensitivity to Rewards. *Current Directions in Psychological Science*, *22*(2), 88–93. https://doi.org/10.1177/0963721413480859

Gillies, G. E., & McArthur, S. (2010). Estrogen Actions in the Brain and the Basis for Differential Action in Men and Women: A Case for Sex-Specific Medicines. *Pharmacological Reviews*, *62*(2), 155–198. https://doi.org/10.1124/pr.109.002071

Hsu, M., Bhatt, M., Adolphs, R., Tranel, D., & Camerer, C. F. (2005). Neural Systems Responding to Degrees of Uncertainty in Human Decision-Making. *Science*, *310*(5754), 1680–1683. https://doi.org/10.1126/science.1115327

Huettel, S. A., Stowe, C. J., Gordon, E. M., Warner, B. T., & Platt, M. L. (2006). Neural Signatures of Economic Preferences for Risk and Ambiguity. *Neuron*, *49*(5), 765–775. https://doi.org/10.1016/j.neuron.2006.01.024

Jentsch, J. D., & Taylor, J. R. (1999). Impulsivity resulting from frontostriatal dysfunction in drug abuse: Implications for the control of behavior by reward-related stimuli. *Psychopharmacology*, *146*(4), 373–390. https://doi.org/10.1007/PL00005483

Joëls, M., Fernandez, G., & Roozendaal, B. (2011). Stress and emotional memory: A matter of timing. *Trends in Cognitive Sciences*, *15*(6), 280–288. https://doi.org/10.1016/j.tics.2011.04.004

Kalbe, F., Bange, S., Lutz, A., & Schwabe, L. (2020). Expectancy Violation Drives Memory Boost for Stressful Events. *Psychological Science*, *31*(11), 1409–1421. https://doi.org/10.1177/0956797620958650

Kessler, R. C., Berglund, P., Demler, O., Jin, R., Merikangas, K. R., & Walters, E. E. (2005). Lifetime Prevalence and Age-of-Onset Distributions of DSM-IV Disorders in the National Comorbidity Survey Replication. *Archives of General Psychiatry*, *62*(6), 593–602. https://doi.org/10.1001/archpsyc.62.6.593

Kilford, E. J., Garrett, E., & Blakemore, S. J. (2016). The development of social cognition in adolescence: An integrated perspective. *Neuroscience and Biobehavioral Reviews*, *70*, 106–120. https://doi.org/10.1016/j.neubiorev.2016.08.016

Kirschbaum, C., Kudielka, B., Gaab, J., Schommer, N., & Hellhammer, D. (1999). Impact of Gender , Menstrual Cycle Phase , and Oral Contraceptives on the Activity of the Hypothalamus-Pituitary-Adrenal Axis. *Psychosomatic Medicine*, *61*, 154–162.

Knight, E. L., Christian, C. B., Morales, P. J., Harbaugh, W. T., Mayr, U., & Mehta, P. H. (2017). Exogenous testosterone enhances cortisol and affective responses to social-evaluative stress in dominant men. *Psychoneuroendocrinology*, *85*, 151–157. https://doi.org/10.1016/j.psyneuen.2017.08.014 LK - http://grlinker.coalliance.org/grlinker/grl000110/grl-TTU.cgi?sid=EMBASE&issn=18733360&id=doi:10.1016%2Fj.psyneuen.2017.08.014&atitle=Exogenous+testosterone+enhances+cortisol+and+affective+responses+to+social-evaluative+stress+in+dominant+men&stitle=Psychoneuroendocrinology&title=Psychoneuroendocrinology&volume=85&issue=&spage=151&epage=157&aulast=Knight&aufirst=Erik+L.&auinit=E.L.&aufull=Knight+E.L.&coden=PSYCD&isbn=&pages=151-157&date=2017&auinit1=E&auinitm

Knight, E. L., & Mehta, P. H. (2016). Hierarchy stability moderates the effect of status on stress and performance in humans. *Proceedings of the National Academy of Sciences*, *114*(1), 78–83. https://doi.org/10.1073/pnas.1609811114

Koski, J., Xie, H., & Olson, I. R. (2015). Understanding Social Hierarchies: The Neural and Psychological Foundations of Status Perception. *Soc Neurosci*, *10*(5), 527–550. https://doi.org/10.1080/17470919.2015.1013223.Understanding

Lago, T., Davis, A., Grillon, C., & Ernst, M. (2017). Striatum on the anxiety map: Small detours into adolescence. *Brain Research*, *1654*, 177–184. https://doi.org/10.1016/j.brainres.2016.06.006

Lennartsson, A., Kushnir, M. M., Bergquist J, Billig H, & Jonsdottir, I. H. (2012). Sex steroid levels temporarily increase in response to acute psychosocial stress. *Int J Psychophysiol*, *84*(3), 246–253.

Ligneul, R., Obeso, I., Ruff, C. C., & Dreher, J. C. (2016). Dynamical Representation of Dominance Relationships in the Human Rostromedial Prefrontal Cortex. *Current Biology*, *26*(23), 3107–3115. https://doi.org/10.1016/j.cub.2016.09.015

Liu, J. J. W., Ein, N., Peck, K., Huang, V., Pruessner, J. C., & Vickers, K. (2017). Sex differences in salivary cortisol reactivity to the Trier Social Stress Test (TSST): A meta-analysis. *Psychoneuroendocrinology*, *82*(April), 26–37. https://doi.org/10.1016/j.psyneuen.2017.04.007

Lupien, S. J., McEwen, B. S., Gunnar, M. R., & Heim, C. (2009). Effects of stress throughout the lifespan on the brain, behaviour and cognition. *Nature Reviews Neuroscience*, *10*(6), 434–445. https://doi.org/10.1038/nrn2639

Marceau, K., Ruttle, P. L., Shirtcliff, Elizabeth Essex, M. J. A., & Susman, E. J. (2014). Developmental and contextual considerations for adrenal and gonadal hormone functioning during adolescence: Implications for adolescent mental health. *Developmental Psychobiology*, *57*(6), 742–768. https://doi.org/10.1002/dev.21214

Marceau, K., Shirtcliff, E. A., Hastings, P., Klimes-Dougan, B., Zahn-Waxler, C., Dorn, L., & Susman, E. J. (2014). Within-adolescent coupled changes in cortisol with DHEA and testosterone in response to three stressors during adolescence. *Psychoneuroendocrinology*, *41*, 33–45. https://doi.org/10.1038/jid.2014.371

Mehta, P. H., & Beer, J. (2010). Neural mechanisms of the testosterone-aggression relation: The role of orbitofrontal cortex. *Journal of Cognitive Neuroscience*, *22*(10), 2357–2368. https://doi.org/10.1162/jocn.2009.21389

Mehta, P. H., & Prasad, S. (2015). The dual-hormone hypothesis: A brief review and future research agenda. *Current Opinion in Behavioral Sciences*, *3*, 163–168. https://doi.org/10.1016/j.cobeha.2015.04.008 LK - http://grlinker.coalliance.org/grlinker/grl000110/grl-TTU.cgi?sid=EMBASE&issn=23521546&id=doi:10.1016%2Fj.cobeha.2015.04.008&atitle=The+dual-hormone+hypothesis%3A+A+brief+review+and+future+research+agenda&stitle=Curr.+Opin.+Behav.+Sci.&title=Current+Opinion+in+Behavioral+Sciences&volume=3&issue=&spage=163&epage=168&aulast=Mehta&aufirst=Pranjal+H.&auinit=P.H.&aufull=Mehta+P.H.&coden=&isbn=&pages=163-168&date=2015&auinit1=P&auinitm=H.

Panagiotakopoulos, L., & Neigh, G. N. (2014). Development of the HPA axis: Where and when do sex differences manifest? *Frontiers in Neuroendocrinology*, *35*(3), 285–302. https://doi.org/10.1016/j.yfrne.2014.03.002

Pouwels, J. L., Lansu, T. A. M., & Cillessen, A. H. N. (2016). Participant roles of bullying in adolescence: Status characteristics, social behavior, and assignment criteria. *Aggressive Behavior*, *42*(3), 239–253. https://doi.org/10.1002/ab.21614

Pruessner, J. C. (2018). ScienceDirect The interplay of sex and gender on the reactivity of the endocrine stress axis in humans. *COBEHA*, *23*, 191–195. https://doi.org/10.1016/j.cobeha.2018.08.003

Purves-Tyson, T. D., Owens, S. J., Double, K. L., Desai, R., Handelsman, D. J., & Weickert, C. S. (2014). Testosterone induces molecular changes in dopamine signaling pathway molecules in the adolescent male rat nigrostriatal pathway. *PLoS ONE*, *9*(3), 1–2. https://doi.org/10.1371/journal.pone.0091151

Rudolph, K. D., Davis, M. M., Telzer, E. H., Troop-Gordon, W., & Miernicki, M. E. (2016). Adding insult to injury: Neural sensitivity to social exclusion is associated with internalizing symptoms in chronically peer-victimized girls. *Social Cognitive and Affective Neuroscience*, *11*(5), 829–842. https://doi.org/10.1093/scan/nsw021

Schoofs, D., & Wolf, O. T. (2011). Are salivary gonadal steroid concentrations influenced by acute psychosocial stress? A study using the Trier Social Stress Test (TSST). *International Journal of Psychophysiology*, *80*(1), 36–43. https://doi.org/10.1016/j.ijpsycho.2011.01.008

Silverman, M. H., Jedd, K., & Luciana, M. (2015). Neural networks involved in adolescent reward processing: An activation likelihood estimation meta-analysis of functional neuroimaging studies. *NeuroImage*, *122*, 427–439. https://doi.org/10.1016/j.neuroimage.2015.07.083

Sinclair, D., Purves-Tyson, T. D., Allen, K. M., & Weickert, C. S. (2014). Impacts of stress and sex hormones on dopamine neurotransmission in the adolescent brain. *Psychopharmacology*, *231*(8), 1581–1599. https://doi.org/10.1007/s00213-013-3415-z

Smith, S. S. (2013). α4βδ GABAA receptors and tonic inhibitory current during adolescence: Effects on mood and synaptic plasticity. *Frontiers in Neural Circuits*, *7*(September), 1–16. https://doi.org/10.3389/fncir.2013.00135

Somerville, L. H., Jones, R. M., & Casey, B. J. (2010). A time of change: Behavioral and neural correlates of adolescent sensitivity to appetitive and aversive environmental cues. *Brain and Cognition*, *72*(1), 124–133. https://doi.org/10.1016/j.bandc.2009.07.003

Spear, L. P. (2000). The adolescent brain and age-related behavioral manifestations. In *Neuroscience and Biobehavioral Reviews* (Vol. 24, Issue 4). https://doi.org/10.1016/S0149-7634(00)00014-2

Steinberg, L. (2004). Risk Taking in Adolescence: What Changes, and Why? *Annals of the New York Academy of Sciences*, *1021*(1), 51–58. https://doi.org/10.1196/annals.1308.005

Steinberg, L., Albert, D., Cauffman, E., Banich, M., Graham, S., & Woolard, J. (2008). Age differences in sensation seeking and impulsivity as indexed by behavior and self-report: Evidence for a dual systems model. *Developmental Psychology*, *44*(6), 1764–1778. https://doi.org/10.1037/a0012955

Steinberg, L., & Chein, J. M. (2015). Multiple accounts of adolescent impulsivity. *Proceedings of the National Academy of Sciences*, *112*(29), 8807–8808. https://doi.org/10.1073/pnas.1509732112

Stroud, L. R., Salovey, P., & Epel, E. S. (2002). Sex differences in stress responses: Social rejection versus achievement stress. *Biological Psychiatry*, *52*(4), 318–327.

Terburg, D., Morgan, B., & van Honk, J. (2009). The testosterone-cortisol ratio: A hormonal marker for proneness to social aggression. *International Journal of Law and Psychiatry*, *32*(4), 216–223. https://doi.org/10.1016/j.ijlp.2009.04.008

Tottenham, N., & Galván, A. (2016). Stress and the adolescent brain: Amygdala-prefrontal cortex circuitry and ventral striatum as developmental targets. *Neuroscience and Biobehavioral Reviews*, *70*, 217–227. https://doi.org/10.1016/j.neubiorev.2016.07.030

Trapp, S., O'Doherty, J. P., & Schwabe, L. (2018). Stressful Events as Teaching Signals for the Brain. *Trends in Cognitive Sciences*, *22*(6), 475–478. https://doi.org/10.1016/j.tics.2018.03.007

Turan, B., Tackett, J. L., Lechtreck, M. T., & Browning, W. R. (2015). Coordination of the cortisol and testosterone responses: A dual axis approach to understanding the response to social status threats. *Psychoneuroendocrinology*, *62*, 59–68. https://doi.org/10.1016/j.psyneuen.2015.07.166

Vaessen, T., Hernaus, D., Myin-Germeys, I., & van Amelsvoort, T. (2015). The dopaminergic response to acute stress in health and psychopathology: A systematic review. *Neuroscience and Biobehavioral Reviews*, *56*, 241–251. https://doi.org/10.1016/j.neubiorev.2015.07.008

Van Anders, S. M., Goldey, K. L., & Kuo, P. X. (2011). The Steroid/Peptide Theory of Social Bonds: Integrating testosterone and peptide responses for classifying social behavioral contexts. *Psychoneuroendocrinology*, *36*(9), 1265–1275. https://doi.org/10.1016/j.psyneuen.2011.06.001

van den Bos, W., & Hertwig, R. (2017). Adolescents display distinctive tolerance to ambiguity and to uncertainty during risky decision making. *Scientific Reports*, *7*(1), 40962. https://doi.org/10.1038/srep40962

van Duijvenvoorde, A. C. K., Peters, S., Braams, B. R., & Crone, E. A. (2016). What motivates adolescents? Neural responses to rewards and their influence on adolescents' risk taking, learning, and cognitive control. *Neuroscience & Biobehavioral Reviews*, *70*, 135–147. https://doi.org/10.1016/j.neubiorev.2016.06.037

Van Leijenhorst, L., Zanolie, K., Van Meel, C. S., Westenberg, P. M., Rombouts, S. A. R. B., & Crone, E. A. (2010). What Motivates the Adolescent? Brain Regions Mediating Reward Sensitivity across Adolescence. *Cerebral Cortex*, *20*(1), 61–69. https://doi.org/10.1093/cercor/bhp078

Vigil, P., del Río, J. P., Carrera, B., Aránguiz, F. C., Rioseco, H., & Cortés, M. E. (2016). Influence of Sex Steroid Hormones on the Adolescent Brain and Behavior: An Update. *The Linacre Quarterly*, *83*(3), 308–329. https://doi.org/10.1080/00243639.2016.1211863

Will, G. J., van Lier, P. A. C., Crone, E. A., & Güroğlu, B. (2016). Chronic Childhood Peer Rejection is Associated with Heightened Neural Responses to Social Exclusion During Adolescence. *Journal of Abnormal Child Psychology*, *44*(1), 43–55. https://doi.org/10.1007/s10802-015-9983-0

Wirth, M. M. (2010a). Beyond the HPA axis: Progesterone-derived neuroactive steroids in human stress and emotion. *Frontiers in Endocrinology*, *2*(AUG), 1–14. https://doi.org/10.3389/fendo.2011.00019

Wirth, M. M. (2010b). Beyond the HPA axis: Progesterone-derived neuroactive steroids in human stress and emotion. *Frontiers in Endocrinology*, *2*(AUG), 1–14. https://doi.org/10.3389/fendo.2011.00019

Wirth, M. M., Meier, E. A., Fredrickson, B. L., & Schultheiss, O. C. (2007). Relationship between salivary cortisol and progesterone levels in humans. *Biological Psychology*, *74*(1), 104–107. https://doi.org/10.1016/j.biopsycho.2006.06.007

Wood, R. I. (2004). Reinforcing aspects of androgens. *Physiology and Behavior*, *83*(2), 279–289. https://doi.org/10.1016/j.physbeh.2004.08.012

Zerbes, G., Kausche, F. M., & Schwabe, L. (2020). Stress-induced cortisol modulates the control of memory retrieval towards the dorsal striatum. *European Journal of Neuroscience*, ejn.14942. https://doi.org/10.1111/ejn.14942