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Striatum on the anxiety map: Small detours into adolescence

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Abstract

Adolescence is the most sensitive period for the development of pathological anxiety. Moreover, specific neural changes associated with the striatum might be related to adolescent vulnerability to anxiety. Up to now, the study of anxiety has primarily focused on the amygdala, bed nucleus of the stria terminalis (BNST), hippocampus and ventromedial prefrontal cortex (vmPFC), while the striatum has typically not been considered as part of the anxiety system. This review proposes the addition of the striatum, a complex, multi-component structure, to the anxiety network by underscoring two lines of research. First, the co-occurrence of the adolescent striatal development with the peak vulnerability of adolescents to anxiety disorders might potentially reflect a causal relationship. Second, the recognition of the role of the striatum in fundamental behavioral processes that do affect anxiety supports the putative importance of the striatum in anxiety. These behavioral processes include (1) attention, (2) conditioning/prediction error, and (3) motivation. This review proposes a simplistic schematic representation of the anxiety circuitry that includes the striatum, and aims to promote further work in this direction, as the role of the striatum in shaping an anxiety phenotype during adolescence could have critical implications for understanding and preventing the peak onset of anxiety disorders during this period.

Keywords

Dopamine; Attention bias; Learning; Conditioning; Prediction error; Motivation

1. Introduction

This review focuses on the contribution of the striatum to the emergence of anxiety disorders in adolescence and to the expression of anxiety symptoms. The link of the striatum to anxiety may seem surprising given the canonical role of this structure in reward processes, which are not usually viewed as part of the root problems of anxiety. However, we will present arguments supporting this anxiety-striatum link, which has clear implications for the prevention and treatment of anxiety disorders. As we develop these arguments, it will become evident that much more research needs to be done. Indeed, this is the reason why we

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feel it is time to draw attention to the potentially critical role of the striatum in the pathogenesis of anxiety.

Up to now, the study of anxiety has primarily focused on the amygdala, bed nucleus of the stria terminalis (BNST), hippocampus (HPC), and prefrontal cortex (PFC) (Calhoun and Tye, 2015; Davis et al., 2010). While associated both anatomically and functionally with these structures (Avery et al., 2014; Calhoun and Tye, 2015; Torrissi et al., 2015), the striatum has not been considered central to the mechanisms underlying anxiety. The amygdala projects to the striatum and BNST (Fudge et al., 2002; Fudge et al., 2004; Novotny, 1977; Roy et al., 2009), and the striatum and BNST are densely interconnected (Avery et al., 2014; Dong and Swanson, 2006; Haber et al., 1990; Torrissi et al., 2015; Wood and Swann, 2005). The cortex also sends efferents directly to the striatum (Calhoun and Tye, 2015; Cisler and Koster, 2010; Liljeholm and O'Doherty, 2012). Finally, the HPC is strongly interconnected with the striatum, especially during context retrieval (Ross et al., 2011). Taken together, these data place the striatum in an ideal position to be part of the anxiety circuit. The goal of this review is to call attention to an area of research that has not been systematically explored to gain a more comprehensive understanding of the neurobiology of anxiety.

Fig. 1A illustrates the classical neural network of anxiety (for review Calhoun and Tye (2015)). Upon exposure to threat, the amygdala receives information directly from the sensory cortex and codes threat valence. Information about the detected threat is then sent to the BNST, ventral HPC (vHPC), and medial PFC (mPFC) to process threat responses. The mPFC and vHPC in turn relay the processed threat information back to the amygdala and BNST as part of a circular loop.

In Fig. 1B, the striatum is included in the anxiety network. In this model, the striatum receives information from the amygdala (BLA) and cortex (mPFC, entorhinal, insular) during threat exposure (for reviews Calhoun and Tye (2015) and Liljeholm and O'Doherty (2012)). Resting state fMRI and DTI studies have documented functional connectivity of the striatum with the HPC and BNST (Avery et al., 2014; Torrissi et al., 2015). However, the role of the BNST-striatum connection in the response to threat remains to be clarified.

Whereas the present work is not directly anchored in the developmental changes associated with adolescence, we hope to highlight the relationship between the high vulnerability of adolescents to anxiety disorders and concurrent striatal developmental plasticity. The striatum is a complex, multi-component structure, which contributes to many fundamental behavioral processes. Several of these processes are critically implicated in anxiety, including (1) attention, (2) conditioning/prediction error, and (3) motivation. As we address these processes, we will make detours into the adolescence period to revisit the role of the adolescent striatal plasticity in the emergence of clinical anxiety. Prior to this, however, we will briefly review general aspects of the adolescent period and striatal function.

2. Adolescence

Adolescence is the transition period linking childhood to adulthood. Behaviorally, typical adolescence is marked by an increase in the search for novelty, sensation and reward. These

changes are thought to be adaptive and meant to facilitate the normative adolescent shift away from the familial nest and towards peer groups. However, they also contribute to the adolescent rise in morbidity and mortality, mainly secondary to deleterious consequences of risky goal-directed behaviors (for review see Spielberg et al. (2014)) and enhanced vulnerability to psychiatric disorders, including those of clinical anxiety (Kessler et al., 2005; Richards et al., 2012).

The prevalence of anxiety disorders during early adolescence is 10–20% (Achenbach et al., 1998; Costello et al., 2003; Shaffer et al., 1996), and lifetime prevalence is 25–29% (Kessler et al., 1994; Kessler et al., 2005). Adolescence represents the most sensitive period for the development of pathological anxiety (Beesdo et al., 2009). Accordingly, anxiety disorders have their peak onset in early adolescence (Kessler et al., 2005; Leonardo and Hen, 2008) with an average age of onset of 11 years (Kessler et al., 2005). In addition, anxiety disorders in adolescence strongly predict anxiety disorders in adulthood (Copeland et al., 2009; Ferdinand et al., 2007), and high trait anxiety persists from childhood into adulthood (Feehan et al., 1993; Ferdinand and Verhulst, 1995; Pine et al., 1998). The gender difference for anxiety susceptibility, with a female preponderance for generalized anxiety, also widens with age (Meeus et al., 2015).

Adolescence witnesses changes at multiple levels of brain organization including molecular, cellular, regional and network (for review see Ernst et al. (2011)). These comprise increases in axon myelination and synaptic pruning, and declines in energy utilization (for reviews Richards et al. (2012) and Spear (2000)), together resulting in heightened efficiency of brain function (for review Ernst and Mueller (2008)). More specific changes affect the striatum, as will be described in the next section (Section 3).

3. Striatum and its networks

The striatum is classically described as the key node of the reward/approach system (for review see Ernst and Spear (2009)). It receives dopaminergic projections from midbrain dopamine nuclei (substantia nigra and ventral tegmental area). Top-down cortical projections relay information to the striatum, which is then dispatched back to the cortex via the thalamus (reviews Ernst and Fudge (2009) and Liljeholm and O'Doherty (2012)).

These cortico-striatal-thalamic-cortical circuits are organized into loops that have been shown to be functionally segregated and integrated along a ventral-dorsal gradient (Alexander et al., 1986; Haber and Knutson, 2010). The dorsal striatum comprises the dorsolateral areas of the caudate nucleus and putamen, and receives input from the prefrontal and parietal cortices (Heimer et al., 2008; Porter et al., 2015). In addition to basic motor functions, the dorsal striatum contributes to cognitive control involved in decision-making and action-initiation (Balleine et al., 2007; Porter et al., 2015). The ventral striatum consists of the shell and core of the nucleus accumbens together with the ventromedial aspects of the caudate nucleus and putamen (for review see Ernst and Fudge (2009)). The ventral striatum receives projections from the amygdala and HPC, as well as the medial orbitofrontal and anterior cingulate cortices (Bolstad et al., 2013; Ernst and Fudge, 2009; Groenewegen et al., 1987; Heimer et al., 2008; Porter et al., 2015). This structure primarily subserves motivation

and learning processes (Cauda et al., 2011; Dayan and Balleine, 2002; O'Doherty et al., 2004; Porter et al., 2015).

The ventral striatum is preferentially linked to the ventral PFC, an area associated with emotion regulation, while the dorsal striatum is connected to premotor, motor, and parietal cortices that regulate motor and cognitive processes (Porter et al., 2015). Although the dorsal striatum is implicated in automatic responses and habit formation, the ventral striatum may be more involved in anxiety, given its importance in emotional processes.

At the molecular level, the dopamine system undergoes significant changes during adolescence, both sub-cortically (striatum) and cortically (prefrontal cortex) (for review Ernst et al. (2009)). Dopamine (DA) regulates behavior via a balance between its tonic and phasic release, which coordinates excitatory and inhibitory neural activity. During adolescence, one-third to one-half of striatal D1 receptors (D1R) and D2 receptors (D2R) are lost (for review Ernst and Spear (2009)). This adolescent decrease in dopamine receptors might be compensated by an increase in binding affinity, which rises by 23 fold from childhood, and then diminishes by 20–40% into adulthood (Tarazi et al., 1999; review Galván (2010)).

At the regional level, gray matter volume across childhood, adolescence and into adulthood shows heterogeneous maturation. Brain maturation can be quantified using measures of gray matter density and volume, both related to myelination, axon volume and neuronal pruning. Most relevant here is the finding that, unlike the parietal, temporal and occipital lobes, striatal gray matter shows maturational changes during adolescence, and not childhood (Galván, 2010; Sowell et al., 1999b). Volumetric measures of caudate nucleus and putamen peak during early adolescence and then decrease during adulthood (Giedd et al., 1996; Giedd et al., 1999), resulting in significantly smaller striatal volumes in adults compared to adolescents (Lenroot et al., 2007; Sowell et al., 1999a).

At the network level, changes in the intrinsic functional connectivity across development have been reported (see review, Ernst et al. (2015)). A recent resting state fMRI study revealed that the intrinsic functional connectivity increased between the dorsal caudate nucleus and posterior cingulate cortex from childhood into adulthood. The study also found decreased connectivity of the ventral striatum with the anterior insula and the dorsal anterior cingulate cortex across this same period (Porter et al., 2015). Finally, adolescent maturation also differs between sexes. This notion is important in the face of the gender difference in anxiety prevalence previously mentioned in Section 2. The effect of sex hormones on the striatum will be discussed in the next section.

4. Effects of sex hormones

Fig. 1C incorporates the effects of sex hormones within the proposed model. Sex steroid hormones influence striatal function, mostly through their modulation of dopamine activity (Bazzett and Becker, 1994; Lewis and Dluzen, 2008). However, this literature is complex for three main reasons. First, reports on the direction of these effects diverge, a fact attributed to a number of factors, including within-studies differences in hormone levels (Becker, 1990;

Clopton and Gordon, 1985), selected striatal sub-regions (Bazzett and Becker, 1994), behavioral contexts (Davis et al., 2005; Galea et al., 2001), and gender (e.g., Becker, 1990; Yoest et al., 2014). For example, estradiol in the striatum is able to acutely enhance DA signaling in females but not males. Second, studies have been conducted mostly in animals, leaving open the question of how findings translate to humans. Furthermore, research has focused preferentially on female rather than male gonadal hormones, leaving more uncertainty about male steroid hormonal effects on striatal function. Third, estrogen, and probably other steroids, have multiple roles and mechanisms of action (e.g., nuclear and non-nuclear), making it difficult to predict specific actions.

Notwithstanding these caveats, data seem to converge on the following facts. Basic research has demonstrated that estrogen and testosterone potentiate striatal dopamine response to sexual activity. In females, striatal dopamine fluctuates with estradiol level across the menstrual cycle, and higher estradiol level is associated with higher dopamine activity, leading to higher motivation to approach (Colzato et al., 2010; Xiao and Becker, 1994).

A few neuroimaging studies in humans have examined levels of gonadal hormones in relation to striatal response to reward (Op de Macks et al., 2011; Hermans et al., 2010; van Honk et al., 2004; Forbes et al., 2010). Interestingly, in contrast to basic research, these studies focused on testosterone rather than estradiol. Similar to the effects of estradiol in animals, testosterone increased striatal response to reward anticipation, however more reliably in males than females (Forbes et al., 2010; Op de Macks et al., 2011).

Taken together, these data have implications for the behavioral changes taken place in adolescence during puberty. These behavioral changes, namely enhanced risk-taking, novelty and sensation seeking, and social salience have been attributed to a rise in striatal/ dopamine sensitivity to novel, rewarding or social stimuli (see review, Ernst and Spear (2009)). Such peak adolescent striatal sensitivity is likely to be facilitated by the massive pubertal surge in gonadal hormone levels, but the nature of the facilitated behaviors may differ between males and females (review Becker (2009)).

So far, we described how the striatum and the main neuro-transmitter of this structure, dopamine, undergo substantial changes during adolescence, a period of high vulnerability for the development of clinical anxiety. In the next sections, we will address processes known to be affected in anxiety and to also be dependent on striatal function per se-8. As a caveat, we will purposely and for the sake of clarity not discuss networks. We will remain regionally-focused, even though the striatum clearly does not function in isolation and the processes reviewed below are mapped to neural circuits.

5. Striatum and attention

“Attention” refers to a multi-faceted process that filters information. Attention permits individuals to orient towards task-relevant stimuli or rules in order to guide optimal behavior (review Shechner et al. (2012)). In anxiety, threat stimuli, real or imaginary, are imbued with heightened salience, which, in turn, determines a “threat attention bias” (Eldar et al., 2010). This “threat attention bias” is defined by a propensity to orient toward, and a difficulty to

switch attention away from, threat stimuli (for reviews see Cisler and Koster (2010) and Mathews et al. (1997)).

Attention bias might explain paradoxical striatal coding of reward value. For example, Benson et al. (2015) reported higher striatal activation to low- than to high-valued outcomes in anxious individuals (a pattern not seen in healthy controls). This indicates that anxious individuals tend to assign greater salience to low rewards than to high rewards, perhaps because of the relative negative value of low vs. higher rewards (Benson et al., 2015).

The striatum, together with dopamine neurotransmission, has been proposed to play a key role in the regulation of attention, particularly through its interaction with the prefrontal and parietal cortices (Choi et al., 2012; Di Martino et al., 2008; Porter et al., 2015; van Schouwenburg et al., 2015). Closely linked to the parietal lobe, the posterior cingulate and precuneus are known to be important modulators of attention (Leech and Sharp, 2014). In humans, levels of the dopamine transporter in the striatum have been shown to affect attention by modulating activation of the precuneus and cingulate gyrus during an attention task (Tomasini et al., 2009).

Developmentally, it has been suggested that attention bias to threat-related stimuli is found in both anxious and non-anxious children. With time, non-anxious children learn to inhibit this bias, but anxious children do not (Kindt et al., 1997a; Kindt et al., 1997b), supporting a growth-related change in the regulation of attention. This change in attention regulation with age may partly reflect changes in striatal function. As mentioned earlier, the intrinsic functional connectivity between the dorsal caudate nucleus and posterior cingulate cortex seems to increase with age (Porter et al., 2015). Such progressively stronger functional links between the dorsal striatum and attention-related structures might contribute to the gain in attention regulation seen during adolescence. Any perturbation in the maturation of this connectivity might be a risk factor for anxiety through deficits in attention regulation.

6. Striatum and conditioning/prediction error

6.1. Conditioning

Fear conditioning is an *associative learning* process that consists of the tagging of threat onto otherwise neutral stimuli, environments, situations or actions, through repeated exposures to the pairing of the neutral event with threat. Two forms of conditioning, classical and instrumental, are identified. Classical (Pavlovian) fear conditioning refers to the pairing of threat with a stimulus (e.g., electrical shock with light), while instrumental conditioning refers to the pairing of threat with an action (e.g., pressing a button to avoid an electrical shock).

Perturbations in fear conditioning have been implicated in the pathogenesis of anxiety for over 80 years (Pavlov and Anrep, 1927). A number of conditioning models of anxiety have emerged based on the nature of the conditioning process being targeted, i.e., fear acquisition, extinction, reinstatement, consolidation, reconsolidation, or retention (Ernst et al., 2011). Among the most popular theories are those of enhanced conditionability and deficits in fear extinction (for review Lissek et al. (2005)), as well as those of stimulus generalization

(Kheirbek et al., 2012; Lissek et al., 2008). In other words, anxiety disorders may present with a generalization of threat tagging onto safe or ambiguous stimuli, an increased reactivity to safety and threat signals, and a resistance of fear reactivity to extinction.

The striatum has long been known to be involved in appetitive conditioning, particularly in the context of addiction (for review see Chambers et al. (2003)). However, it also contributes to aversive learning (reviews Brooks and Berns (2013) and Delgado et al. (2008)). Basic research in non-human animals suggests that the striatum, a critical structure in goal-directed behavior (Atallah et al., 2007; Balleine et al., 2007; Cardinal et al., 2003), specifically facilitates the acquisition (i.e., learning) of avoidance actions that diminish exposure to a fear-eliciting event (Ledoux and Gorman, 2001). Avoidance actions to threat stimuli can be either passive (reflexive, e.g., freezing), or active (reflective, e.g., retreating to a safe place). Recent work shows the involvement of the ventral striatum particularly in active avoidance (Darvas et al., 2011). On the other hand, the role of the dorsal striatum in fear conditioning is uncertain (for review see White (2009)). Evidence suggests the involvement of sub-regions of the dorsal striatum in habitual and goal-directed instrumental conditioning (reviews Balleine et al. (2009) and Liljeholm and O'Doherty (2012)).

Most developmental data about functional striatal changes associated with conditioning, similarly to the bulk of work on general conditioning, concern appetitive conditioning. These data suggest a unique enhancement of reward learning during adolescence across species (see reviews Eppinger et al. (2011) and Ernst et al. (2011)). In addition, recent data support a role of steroid sex hormones in striatal responses to reward (Forbes et al., 2010), suggesting that puberty-related hormonal changes might contribute to the reported heightened appetitive conditioning in adolescents (see Section 4 on sex hormones). Whether similar adolescent changes in aversive conditioning related to striatal functional maturation also exist remains to be tested.

In fact, very few developmental studies have focused on the potential ontogenic changes in fear conditioning during adolescence (see review Ernst et al. (2011)). A fairly recent study directly compared adolescents (13 years old) and young adults (28 years old), and revealed reduced fear-cue discrimination between safe and threat in the adolescent group (Lau et al., 2011). This finding only emerged in the fMRI environment, a relatively anxiogenic situation, and was not seen in the clinic. While non-human animal work can provide helpful data, surprisingly, despite decades of basic neuroscience research in fear conditioning, few studies have tested adolescent subjects with younger and older comparison groups (for reviews see Pattwell et al. (2013) and Quirk et al. (2010)). One such study examined pre-juvenile, juvenile and adult mice, and tested context-conditioning and cue-conditioning, as well as acquisition vs. retrieval of the conditioned behavior (Pattwell et al., 2011). Mice of all ages evidenced cue-conditioned fear. However, the mice conditioned in early adolescence (29 days of age) failed to show context-conditioned fear, in contrast to the younger (23 days of age) or older mice (39, 49, or 79 days of age), who exhibited the expected freezing response in a shock-paired context. Both human and animal studies described above suggest that fear conditioning might undergo unique changes in adolescence. Here again, these changes might partly be fostered by striatal development.

6.2. Prediction error

The best evidence for a role of the striatum in conditioning comes from prediction error studies. The prediction error (PE) model is a computational framework applied to reinforcement learning (conditioning). It is used to study the neural mechanisms implicated in incentive learning and goal-directed behavior. Therefore, PE represents a facet of conditioning. PEs are computed values of the difference between the *received* outcome absolute value vs. the *expected* outcome absolute value. PEs are defined by the type of stimuli and the value of the difference value: the type of stimuli can be either rewards (appetitive) or punishments (aversive) and the value can be either positive (greater reward or punishment than expected) or negative (lower reward or punishment than expected). For example, John expects a D score on a test he thought was difficult. He received an A. The prediction error is the affective difference between the expected D and the obtained A. Taken together, four categories of PEs can be identified, (1) positive appetitive PEs (greater reward than expected), (2) negative appetitive PEs (lower reward than expected), (3) positive aversive (higher punishment than expected), and (4) negative aversive PEs (lower punishment than expected).

PE, or the [received – expected] difference value, constitutes a teaching signal by which stimulus-outcome associations are learned. Single-unit electrophysiology studies have shown that this teaching signal, at least for appetitive PE, is computed at the level of dopamine neurons, and is carried by the dopaminergic phasic activity (Schultz et al., 1997; Schultz, 2007). Furthermore, neuroimaging studies in humans indicate that these signals depend heavily on the functional integrity of the striatum (Iordanova, 2009; O'Doherty et al., 2004; Schonberg et al., 2007). Whereas the neural substrates of appetitive PE have been intensely investigated, studies of aversive PE are scarcer (see review Brooks and Berns (2013)).

Theoretically, a negative aversive PE (received punishment smaller than expected) bears a close psychological relationship with a positive appetitive PE (received reward larger than expected reward). Studies of appetitive and aversive PEs report inconsistent findings with regards to the striatum. Some studies find striatal activation to both positive appetitive PEs and positive aversive PEs (Seymour et al., 2007), while others find deactivation to positive-aversive PE signals (Delgado et al., 2000). Most studies support striatal activation by appetitive PEs (Nieuwenhuis et al., 2005a; Nieuwenhuis et al., 2005b; Schonberg et al., 2007), although the site of activation may vary. Some note prominent activation within the dorsal striatum (Delgado et al., 2000) and some within the ventral striatum (Yacubian et al., 2006). Furthermore, striatal activations are reported in more posterior and dorsal striatal regions for aversive PEs compared to appetitive PEs (Seymour et al., 2007). Taken together, this literature supports the PE model for aversive reinforcement learning, such as threat conditioning, but findings are somewhat inconsistent with regard to the direction of the striatal signal of aversive PEs.

As reviewed above, changes in aversive conditioning in adolescence still need to be clarified. Studies of aversive PE across adolescence might shed light on this question. However, at present, only one study has directly examined PE across development, but this study focused selectively on appetitive PE (Cohen et al., 2010). Three age groups (children, adolescents

and adults) were compared on a probabilistic learning task. The adolescent group showed a hypersensitive striatal response to a positive PE at outcome (actual reward greater than expected) relative to adults or children. The question of how adolescents process aversive PEs remains untouched.

Finally, the relationship of this PE-related striatal neural signal to anxiety has not been systematically investigated. There is some suggestion that stress in healthy adults potentiates aversive PE in the ventral striatum (Robinson et al., 2013). In adolescents, one study examined the influence of a history of behavioral inhibition on striatal responses to negative outcomes (Helfinstein et al., 2011). Behavioral inhibition, a temperament that heralds risk for anxiety disorders, was associated with enhanced caudate response to negative but not positive outcome, suggesting a potential hypersensitivity to punishment, and perhaps to aversive PE, in this adolescent group at risk for anxiety.

7. Striatum and motivation

Motivation can be defined as the intensity of drive, or the willingness to spend resources or exert efforts to reach a goal (review Ernst and Spear (2009)). Standard ways to study motivation involve either decision-making tasks, requiring individuals to execute a decision (e.g., button press), or reward tasks, like the monetary incentive delay task which requires individuals to press a button quickly enough to receive a reward (Knutson et al., 2000).

The study of motivation has most often been conducted in the context of addiction (Chambers et al., 2003; Kelley, 2004; Martin et al., 2002), and is not a typical question for anxiety research. However, we will contend in this review that perturbations in motivation might actually also underlie aspects of anxiety, such as the “motivation to avoid.” In the same way that the striatum becomes overly activated by the motivation to acquire drugs, the striatum may become overactive by the motivation to avoid danger. Risk avoidance, which is defined as the avoidance of stimuli or situations with uncertain outcomes, is at the core of anxiety disorders (Lorian and Grisham, 2011; Maner et al., 2007). Similarly, the personality trait of harm avoidance, defined as a proclivity to respond intensely to aversive stimuli and to learn to passively avoid punishment, novelty, or frustrating non-reward is highly associated with anxiety (Cloninger et al., 1993; Montag et al., 2010). The motivation to avoid potentially negative outcomes is thus abnormally high in anxious individuals. This behavioral pattern might have its origin in ventral striatal dysfunction. Indeed, the ventral striatum has long been recognized as a central node of the motivation system (Mogenson et al., 1980; Reinstein et al., 1982). Both appetitive and fearful motivation involve dopamine and glutamate in the nucleus accumbens (for review Carlezon and Thomas (2009)). Motivational valence may be coded along a rostrocaudal gradient, with rostral areas of the nucleus accumbens shell mediating approach behavior, and caudal mediating avoidance behavior (Richard and Berridge, 2011). Interestingly, this gradient demonstrates plasticity in animal models, as calming or stressful environments can shift functional anatomy (for review Helfinstein et al. (2012)).

A number of normative developmental studies have examined the influence of age on striatal function in the context of motivation to obtain a reward (see review Richards et al. (2012)).

Most studies concur on identifying adolescence as a distinct period of peak striatal response to either the preparation for action to obtain a reward or the receipt of the reward (Galván et al., 2006; Geier et al., 2010; Hardin and Ernst, 2009). Therefore, although mostly associated with the pursuit of a reward, these studies seem to show heightened striatal sensitivity to motivated action during the adolescent period (Bar-Haim et al., 2009; Guyer et al., 2006; Helfinstein et al., 2011). This finding is consistent with the notion of adolescence as a high risk-taking period when individuals seek novelty and uncertainty (Ernst et al., 2006; Galván et al., 2006; Steinberg, 2004). The study of “motivation to avoid” in adolescence deserves more research, particularly given its implications for understanding more comprehensively not only the pattern of motivated behaviors in adolescence, but also adolescent vulnerability to anxiety disorders.

The influence of anxiety on motivation tasks, mainly reward-based tasks, has begun to be examined in studies that reveal an anxiety-related hyperactive striatal response to motivated behavior (Bar-Haim et al., 2009; Guyer et al., 2012; Helfinstein et al., 2011). Most studies do not distinguish the motivation to receive a reward from the motivation to avoid a loss. However, individuals with anxiety have been found to be more sensitive to potential losses, but to perform similarly on potential gains compared to non-anxious individuals (Richards et al., 2015). Inhibited adolescents characterized by an early history of behavioral inhibition (i.e., at risk for developing anxiety disorders) also present hyper-activation of the ventral striatum when they perceive that their choices will directly affect anticipated outcomes (Bar-Haim et al., 2009; Guyer et al., 2012; Helfinstein et al., 2011). Taken together, these data support the notion that anxious adolescents, or those at risk for anxiety, have a bias for avoiding negative outcomes compared to receiving a reward. This bias may be ascribed to high motivation to avoid, which can contribute to risk aversion, threat bias, and/or behavioral avoidance (Benson et al., 2015; Galván and Peris, 2014; Helfinstein et al., 2011). Overall, the implication of motivation processes in anxiety calls for a primary involvement of striatal function in the pathogenesis of anxiety.

8. Conclusion

This review focused solely on the role of the striatum in anxiety, and surveyed a large amount of research. Behavioral links between anxiety and striatal function were used as evidence of this link. Three key behavioral domains were addressed, (1) attention, (2) fear conditioning/prediction error, and (3) motivation, because they are both altered in anxiety and dependent on striatal function. Beyond these links, we also noted strong parallels in the developmental trajectories characterizing the onset of anxiety and the ontogeny of striatal function. Adolescence appears to be the most vulnerable period for the emergence of anxiety, which, as this review suggests, might be at least partly related to ontogenic changes in striatal function, independently or potentiated by the pubertal rise in gonadal hormones.

It is important to reiterate the following caveat. The selective focus on the striatum was meant to draw attention to this structure as one of the critical hubs of anxiety circuitry, along with the traditional nodes of this circuit, including amygdala, BNST, hippocampus and vmPFC. Intentionally, the consideration of striatal circuitry vs. anxiety circuitry has been omitted. Integrating the striatum within the classical circuitry of anxiety deserves a review

on its own. In contrast, here we proposed a simplistic schematic of this circuitry in Fig. 1A, to which we add the striatum in Fig. 1B, as a first elementary model for the claim made in this review. We added the contribution of gonadal hormones to the schematic in Fig. 1C, although it is clear the pubertal hormonal surge is likely to affect most of the nodes of the anxiety circuitry.

In summary, the role of the striatum in shaping the neural functional architecture that yields an anxiety phenotype during adolescence could have critical implications for understanding and preventing the peak onset of anxiety disorders during this period, and subsequent consequences in adulthood. Future studies should aim to selectively manipulate striatal function and examine effects on anxiety. Striatal manipulation can be done pharmacologically, for example with dopaminergic agents, or behaviorally, with motivational tasks, while anxiety can be examined in anxiety patients, or via experimental anxiety induction. Given the impact of gonadal hormones on striatal function, a third layer of manipulation is that of gonadal hormones, particularly across puberty.

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Fig. 1.

Fig. 1A illustrates the classical neural network of anxiety (Calhoon and Tye, 2015; Cho et al., 2013; Torrisi et al., 2015). Upon exposure to threat, the amygdala (BLA) receives information directly from the cortex and codes threat valence. Information about the detected threat is then sent to the bed nucleus of the stria terminalis (BNST), hippocampus (vHPC), and cortex (mPFC) for further evaluation. The mPFC and vHPC send threat information back to the amygdala and BNST as part of a circular loop. Not shown are the nuclei within the septum, hypothalamus and brainstem. In Fig. 1B, the striatum is included

in the anxiety network (Avery et al., 2014; Calhoun and Tye, 2015; Cho et al., 2013; Fudge et al., 2002; Groenewegen et al., 1987; Liljeholm and O'Doherty, 2012; Torrisi et al., 2015). In this model, the striatum receives information from the amygdala (BLA) and cortex (mPFC, entorhinal, insular) during threat exposure. The BNST and hippocampus have been shown to be functionally connected to the striatum in animal and resting state fMRI/DTI studies. In Fig. 1C, the potentiating effect of estrogen and testosterone on striatal dopamine response in the context of strong incentives is added to the model. The unique contribution of gonadal hormones, particularly during puberty, to the modulation of striatal function remains by and large unknown, particularly in the context of the anxiety circuitry. In this regard, pubertal hormonal changes are expected to impact other nodes of the anxiety circuitry, an additional layer of complexity that is outside of the scope of this paper.