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Anxious to see you: Neuroendocrine mechanisms of social vigilance and anxiety during adolescence

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Abstract

Social vigilance is a behavioral strategy commonly used in adverse or changing social environments. In animals, a combination of avoidance and vigilance allows an individual to evade potentially dangerous confrontations while monitoring the social environment to identify favorable changes. However, prolonged use of this behavioral strategy in humans is associated with increased risk of anxiety disorders, a major burden for human health. Elucidating the mechanisms of social vigilance in animals could provide important clues for new treatment strategies for social anxiety. Importantly, during adolescence the prevalence of social anxiety increases significantly. We hypothesize that many of the actions typically characterized as anxiety behaviors begin to emerge during this time as strategies for navigating more complex social structures. Here, we consider how the social environment and the pubertal transition shape neural circuits that modulate social vigilance, focusing on the bed nucleus of the stria terminalis and prefrontal cortex. The emergence of gonadal hormone secretion during adolescence has important effects on the function and structure of these circuits, and may play a role in the emergence of a notable sex difference in anxiety rates across adolescence. However, the significance of these changes in the context of anxiety is still uncertain, as not enough studies are sufficiently powered to evaluate sex as a biological variable. We conclude that greater integration between human and animal models will aid the development of more effective strategies for treating social anxiety.

KEYWORDS

bed nucleus of the stria terminalis, oxytocin, prefrontal cortex, stress, testosterone

1 | INTRODUCTION

Anxiety disorders are the most commonly diagnosed mental illness, with 20% of adults experiencing an anxiety disorder within their lifetime. Available treatments such as benzodiazepines (Cassano, Rossi, & Pini, 2002) and selective serotonin reuptake inhibitors (Baldwin, Woods, Lawson, & Taylor, 2011) are widely prescribed, but many patients do not experience remission using these therapeutics. Identification of underlying mechanisms contributing to anxiety could lead to novel approaches for individuals who do not respond to existing treatments. Studies of behavior related to anxiety in non-human animals have already yielded important discoveries of relevant brain circuits and neurochemical systems (Calhoon & Tye, 2015; Cryan &

Abbreviation: BNST bed nucleus of the stria terminalis

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Holmes, 2005; Davis, Walker, Miles, & Grillon, 2010). Most of the approaches used to identify these systems include tasks that involve exploration of novel environments, in the absence of social cues. Different behavioral strategies could be engaged in social contexts, which may have special relevance for social anxiety.

For example, social avoidance and social vigilance are two important components of social anxiety. Social avoidance refers to behavioral withdrawal in a novel social context and may be a protective response to avoid aggressive individuals. Prior research has focused on social avoidance, perhaps due to its role in preventing normal functioning in humans. In this review, we consider the role of social vigilance, which consists of increased monitoring of social cues, often while simultaneously avoiding social contexts. Understanding the underlying mechanisms of social vigilance could provide new insights into how social anxiety disorder develops. Based on work in non-human animals, we propose that vigilance is a coping strategy that increases in adverse or changing social environments (Figure 1). Leading risk factors for social anxiety disorders are tied to either adverse or changing social environments. In particular, we will review studies in animals showing that social vigilance may be effective for exploiting opportunities in a changing social environment. However, in humans prolonged expression of social vigilance may be problematic, leading to increased risk of anxiety disorders (Silvers et al., 2017). Identifying the underlying mechanisms of social vigilance may help explain why rates of anxiety disorders are higher in women than in men (Hollingworth, Burgess, & Whiteford, 2010; Wesselhoeft, Pedersen, Mortensen, Mors, & Bilenberg, 2015). There are likely multiple factors contributing to this sex difference involving an interplay of biological, cultural and experiential factors (Altemus, Sarvaiya, & Neill Epperson, 2014). However, an important clue comes from demographic data showing that sex differences in the prevalence of social anxiety emerge during adolescence (Figure 2; Beesdo et al., 2007; Wesselhoeft et al., 2015). This period is characterized by physiological sexual differentiation and dynamic changes in the social environment, such as moving into a new social group. Social interactions become more salient (Walker et al., 2017), with some evidence in humans that this effect is more pronounced in girls (Guyer, McClure-Tone, Shiffrin, Pine, & Nelson, 2009). The pubertal transition triggers changes in brain structure and function through gonadal hormone-dependent (Schulz & Sisk, 2016) and hormone-independent (Paul, Probst, Brown, & Vries, 2018) mechanisms. These changes may modulate susceptibility to social anxiety (Davey, Yücel, & Allen, 2008). Additionally, stressful social interactions during adolescence can have exaggerated effects on brain structure and function (Romeo, 2017; Rowson et al., 2019). Historically, animal models for studying mechanisms related to anxiety were strongly biased toward males. Increasing representation of females in animal models of anxiety is likely to provide key insights into sex differences in the prevalence of anxiety (McCarthy, Woolley, & Arnold, 2017; Shansky & Woolley, 2016).

In this review, we examine studies in animal model systems that show how social vigilance allows individuals to avoid confrontations yet capitalize on beneficial changes in the social environment. Mechanistically, we focus on the role of the bed nucleus of the stria terminalis, a component of the extended amygdala that is receiving increased attention for its role in modulating anxiety in both human and non-human animals. Intriguingly, in mice social opportunity is associated with increased engagement of the frontal cortex (Williamson, Klein, Klein, Lee, & Curley, 2019). The prefrontal cortex undergoes major structural and functional changes during adolescence, a period during which anxiety rates increase at a faster rate in women than in men. Throughout this review, we consider how adolescent development shapes social vigilance and anxiety. Our review touches on tantalizing clues that may contribute to new perspectives on the development of anxiety disorders, but also reveals major gaps in understanding.

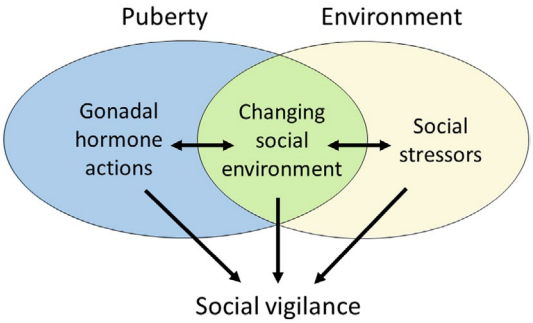

FIGURE 1 During puberty, gonadal hormones shape brain development as an individual adapts to a changing social environment. A dynamic social environment can introduce challenging social conditions. Evidence in non-human animals suggests that social vigilance may be a strategy for coping with adverse social environments while waiting for better opportunities in the social environment

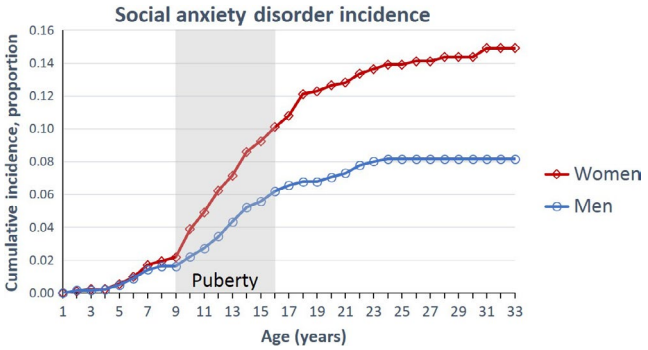

FIGURE 2 Lifetime cumulative incidence estimates for social anxiety disorder. Figure redrawn with permission based on data from Beesdo et al. (2007)

2 | SOCIAL ENVIRONMENT CAN REGULATE THE TIMING OF PUBERTY

A major theme of this review is how adolescence shapes how an individual copes with the social environment. However, there is strong evidence that the timing of pubertal development is highly sensitive to the social environment itself. Low social status delays puberty in marmosets (Abbott & Hearn, 1978; Ginther, Carlson, Ziegler & Snowdon, 2002), rhesus monkeys (Bercovitch, 1993) and baboons (Onyango, Gesquiere, Altmann & Alberts, 2013). Mechanistic studies in naked mole rats suggest that socially induced delay in puberty is mediated by decreased gonadotropin action. Hypothalamic RFamide-related peptide-3 (RFRP-3) is a potent inhibitory modulator of GnRH action (Zhou et al., 2013) and is elevated in subordinate naked mole rats, while exogenous RFRP-3 treatment inhibited sexual and dominance behaviors (Peragine et al., 2017). The removal of the dominant female triggers ovarian cycles in subordinate females within a week (Margulis, Saltzman, & Abbott, 1995). Less dramatic transitions have been observed in mice (Koyama & Kamimura, 1999; Williamson, Lee, et al., 2019). Within 3 min of the removal of a dominant male, subdominant male mice responded with increases in aggressive behavior and within 1 hr show increased GnRH mRNA levels in the medial preoptic area (Williamson, Romeo, & Curley, 2017). Similar changes occur in male cichlid fish after acquiring a new territory (Burmeister, Jarvis, & Fernald, 2005; Maruska & Fernald, 2018). Socially ascending male mice also had increased immediate early gene expression in hypothalamic and limbic brain regions linked to the modulation of social behavior, including infralimbic and prelimbic regions of frontal cortex (Williamson, Klein, et al., 2019). Animal studies show how the social environment can cause changes in brain activity and pubertal timing. Correlational data from humans echo these.

In humans, associations between the social environment and pubertal timing are complex. On the one hand, there is a well-replicated finding that adverse social experiences such as harsh parenting and maltreatment (including physical and sexual abuse) are linked to accelerated pubertal onset, particularly for females (Belsky et al., 2007; Boynton-Jarrett et al., 2013; Noll et al., 2017). Early menarche has been linked to increased risk of anxiety and depression (Colich et al., 2019; Mendle, 2014). In contrast, experiences of deprivation such as poverty and food insecurity are linked to delayed pubertal maturation (Sumner, Colich, Uddin, Armstrong, & McLaughlin, 2019). Currently, the mechanisms through which the social environment modulates the timing of puberty in humans are unclear. However, the effects of exposure to violence are thought to be mediated by threat-response systems, whereas the delay of puberty observed in food insecurity is theorized to be a response to limited bioenergetic resources (Ellis, Figueredo, Brumbach, & Schlomer, 2009). Social status impacts the timing of puberty by regulating gonadotropin function, and in some cases opportunities in the social environment trigger rapid development. How are these opportunities detected? In the next section, we consider social vigilance as a strategy to remain cognizant of changes in the environment while avoiding social conflicts.

3 | SOCIAL ANXIETY AND VIGILANCE AS BEHAVIORAL STRATEGIES FOR ADVERSE SOCIAL ENVIRONMENTS

Exposure to adverse social contexts induces evolutionarily conserved behavioral and physiological responses. One of the most robust observations is that individuals that lose aggressive encounters avoid novel social contexts, a behavior referred to as social avoidance. The phenotype has been observed in rodents (Blanchard, McKittrick, & Blanchard, 2001; Huhman, 2006), birds (Carere, Welink, Drent, Koolhaas, & Groothuis, 2001) and primates (Shively, Laber-Laird & Anton, 1997). This response may allow individuals to avoid engaging in energetically costly and potentially dangerous contests with little opportunity of winning (Neat, Taylor, & Huntingford, 1998). This can be an effective short-term strategy, but social avoidance does not provide an obvious route for enhancing social status. Social vigilance, in which individuals avoid yet monitor unfamiliar social contexts, may be a key behavioral mechanism that allows individuals to seize opportunities when the social environment changes (Figure 3). Social vigilance can be quantified as orienting behavior in a laboratory social interaction test when a focal animal orients toward, but avoids, an unfamiliar individual confined to a small cage (Duque-Wilckens et al., 2018; Williams et al., 2018). If orienting behavior is not observed when the stimulus animal is absent, this demonstrates the social nature of the response. Social vigilance can take other forms, such as the "stretch-attend" posture, which consists of orienting toward a threat while maintaining a crouched posture that reduces visibility. Stretch-attend postures are evoked by social threats (McCann & Huhman, 2012; Morrison, Curry, & Cooper, 2012) and predator cues (Hubbard et al., 2004). Vigilance can also take the form of visual scanning, during which an individual forgoes other activities such as feeding. This form of social vigilance is elevated in low-status individuals of avian (Ekman, 1987), marsupial (Blumstein, Daniel, & Evans, 2001) and primate (Shepherd, Deaner, & Platt, 2006) species. Social vigilance usually coincides with social avoidance, but social avoidance can occur in the absence of social vigilance. These distinct behavioral phenotypes may be driven by distinct mechanisms (see Section 5).

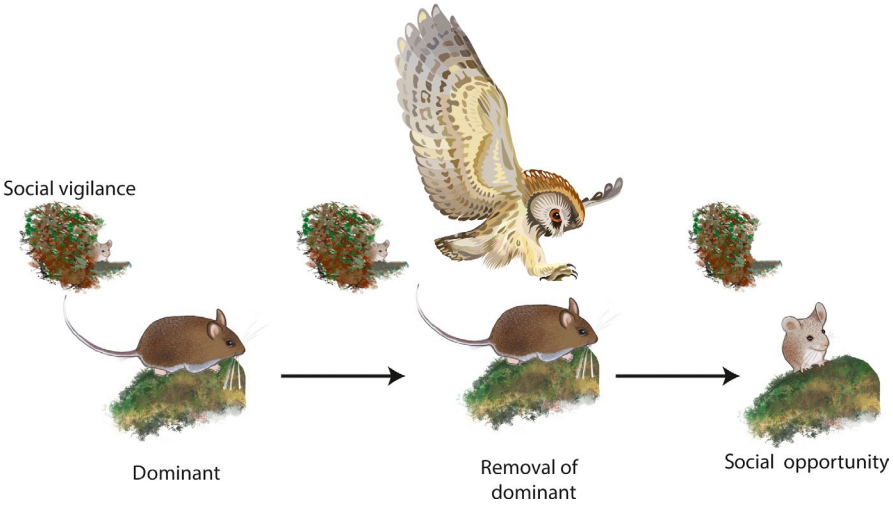

FIGURE 3 Hypothesized use of social vigilance by lower social status individuals. Data from rodents and fish suggest that lower status individuals avoid and monitor the activities of more dominant individuals. If a dominant individual is removed through predation or illness, information gained through social vigilance allows individuals to exploit new opportunities in the social environment. Mouse drawings by Natalia Duque-Wilckens

In humans, individuals with high trait anxiety initially react more quickly to aversive images, suggesting an enhanced state of vigilance (Mogg, Bradley, Miles, & Dixon, 2004). Importantly, increased vigilance combined with social avoidance are key components of behavioral inhibition (Kagan, Reznick, & Snidman, 1987), a temperamental predisposition in humans that appears early in development as reticence to approach unfamiliar people or objects (Henderson, Pine, & Fox, 2015). Behavioral inhibition is the strongest predictor for onset of social anxiety disorders in adulthood (Clauss & Blackford, 2012). Importantly, behavioral inhibition only translates into later anxiety disorders in the presence of additional risk factors, such as adverse social experiences including victimization by peers or low social status within one's peer group (Rubin, Coplan, & Bowker, 2009).

Socioeconomic status is a proxy measure of social position in human society and is linked to behavioral, cognitive and neural indices of vigilance to social threat in childhood (Boyce et al., 2012; Chen & Matthews, 2001), adolescence (Chen, Langer, Raphaelson, & Matthews, 2004; Inderbitzen, Walters, & Bukowski, 1997) and adulthood (Cundiff, Smith, Baron, & Uchino, 2016; Gianaros et al., 2008; Kraus, Horberg, Goetz, & Keltner, 2011). Importantly, some evidence suggests that low socioeconomic status may be associated with heightened vigilance to only social and not non-social threats (Hostinar, Ross, Chan, Chen, & Miller, 2017). Furthermore, loneliness (i.e. subjective social isolation) is associated with enhanced rather than decreased monitoring of social cues (Gardner, Pickett, Jefferis, & Knowles, 2005; Vanhalst, Gibb, & Prinstein, 2017). In this way, human social vigilance closely resembles the combination of social attention and avoidance observed in rodents exposed to social stress. It has been theorized that enhanced social monitoring may operate as a strategy for coping with and improving one's social status (Pickett & Gardner, 2005). Taken together, these findings underscore the critical need to assess whether social vigilance has a strategic role for coping with low social status. Interestingly, adolescent development is frequently characterized by new opportunities to transition from lower to higher social status.

4 | SOCIAL STATUS AND ADOLESCENT DEVELOPMENT

We hypothesize that social vigilance could be an important behavioral strategy used during adolescence to cope with lower social status, as it is common for adolescents to have lower social status than older, more established adults. In rhesus macaques, older adults easily gained social dominance in a new social group by social posturing, which led to avoidance by the smaller/younger members (Bernstein & Mason, 1963). In stable social groups, older adults have the advantage of developed relationships of peer support against younger challengers (Gartlan, 1968). Age is also a good predictor of social status in rodents. Analyses of a large group (30–50) of rats in a laboratory colony found that increased age was a better predictor of social status than body weight (Macdonald, Berdoy, & Smith, 1995). Similar results were observed in colonies of rats living outdoors. Younger males only increased social status after older males had succumbed to predation (Adams & Boice, 1983). A key contributing mechanism to the effects of experience may be the winner effect. The winner effect is a phenomenon wherein males that win an aggressive encounter show higher levels of aggression in future encounters and an increased likelihood of winning future contests (Franz, McLean, Tung, Altmann, & Alberts, 2015; Lehner, Rutte, & Taborsky, 2011; Oyegbile & Marler, 2005; Marler & Trainor, in press). In males, the experience of winning an aggressive encounter is coupled with a temporary spike in testosterone levels in the winning male, after the victor has been determined (Oyegbile & Marler, 2005; Wingfield

& Wada, 1989). Males deprived of this post-winning testosterone spike do not show future increases in aggressive behavior (Trainor, Bird, & Marler, 2004). It is important to note that these studies focus exclusively on adult males. Adolescents have less time to win aggressive encounters than adults, and thus less time to build up the positive reinforcement of aggressive behavior associated with the winner effect. Thus, less experience, lower aggression levels and reduced social support are possible factors that can put an adolescent animal at a social disadvantage compared with already established adults. We hypothesize that observation of social dynamics through social vigilance and other behaviors could be a key behavioral strategy used by adolescents as they try to eke out the foundations of their own social status. Watching and waiting for a social opportunity, as documented in studies of cichlid fish (Burmeister et al., 2005; Maruska & Fernald, 2018) and mice (Williamson, Klein, et al., 2019; Williamson et al., 2017), could be an important strategy for adolescents. However, exaggerated social vigilance expression could contribute to increased risk of anxiety disorders (Clauss & Blackford, 2012).

5 | THE BED NUCLEUS OF THE STRIA TERMINALIS AS A MODULATOR OF SOCIAL VIGILANCE

The bed nucleus of the stria terminalis (BNST) is a key component of neural circuits modulating behavioral responses to threat (Trainor et al., 2004). The BNST is ideally suited to modulate social vigilance because of its strong connections with the social behavior network (O'Connell & Hofmann, 2011) as well as extended amygdala circuits that modulate responses to threat. Our understanding of how the BNST controls behavioral responses to threats has evolved over time. Early work suggested a dissociation between the BNST and the central nucleus of the amygdala, with the BNST modulating responses to more diffuse threats and the central nucleus of the amygdala being more important for more defined threats (e.g. a conditioned cue; Walker & Davis, 1997). More recent data suggest more overlap in function, and imaging studies often show coordinated responses between BNST and central nucleus of the amygdala (Daniel & Rainnie, 2016; Davis et al., 2010). Imaging data from hundreds of rhesus monkeys (Oler et al., 2010) and human participants (Avery, Clauss, & Blackford, 2016; Yassa, Hazlett, Stark, & Hoehn-Saric, 2012) also show that threat exposure increases activity within the BNST. It has been hypothesized that the BNST may assign a valence to ambiguous social contexts based on prior experience (Lebow & Chen, 2016). Data from the California mouse social defeat model are consistent with this idea (Duque-Wilckens et al., 2018).

Studies on the California mice point to the BNST as a key modulator of social vigilance (Duque-Wilckens et al., 2018). In this monogamous species, both males and females are aggressive, which allows for the study of social stress in both sexes (Steinman & Trainor, 2017). In adult females but not males, social stress increased expression of brain-derived neurotrophic factor within the BNST and infusion of a tyrosine kinase B receptor (the main receptor for brain-derived neurotropic factor) antagonist into the BNST restored normal social approach behavior in stressed females (Greenberg et al., 2014). These results suggest that social stress may induce synaptic plasticity within the BNST. In the BNST, studies of male rodents show that repeated stressors can enhance excitatory neurotransmission in some cell types (Dabrowska et al., 2013) while reducing excitability in other cell types (McElligott et al., 2010). The BDNF findings in California mice suggest that there could be important sex differences in stress-induced synaptic plasticity. A likely candidate pathway is the oxytocin system.

In adult female but not male California mice, social stress has long-term effects on oxytocin neurons within the ventral BNST (Steinman et al., 2016). Oxytocin is usually assumed to be produced within the hypothalamus, but oxytocin-producing neurons are present in the BNST of mice (Nasanbuyan et al., 2018), rats (DiBenedictis, Nussbaum, Cheung, & Veenema, 2017), prairie voles (Kelley, Saunders, & Ophir, 2018) and marmosets (Wang, Moody, Newman, & Insel, 1997). Social stress has enduring effects on the reactivity of oxytocin neurons. Ten weeks after a final stress exposure, females had more oxytocin/c-fos colocalizations than controls following exposure to novel environment, even in the absence of social cues (Steinman et al., 2016). This suggests that stress enhances the reactivity of BNST oxytocin neurons in novel environments. Intriguingly, when tested in a novel environment, infusion of an oxytocin receptor antagonist into the anteromedial BNST reduced social vigilance in stressed females and increased social approach (Duque-Wilckens et al., 2018). Impressively, a systemic injection of oxytocin receptor antagonist had identical results. To achieve the same effect with a selective serotonin reuptake inhibitor, 4 weeks of daily treatment was required (Greenberg et al., 2014). Although oxytocin is normally considered a neuropeptide that enhances social approach, many studies show that oxytocin can induce social avoidance and anxiety (Beery, 2015; Eckstein et al., 2014), especially in females. Together, these results suggest that oxytocin enhances the salience of both positive and aversive social interactions (Shamay-Tsoory & Abu-Akel, 2016). Context-dependent effects of oxytocin may be mediated by distinct neural circuits that promote either social approach or social vigilance (Steinman,

Duque-Wilckens, & Trainor, 2019). Indeed, stress-induced vigilance can be observed in the absence of alterations in social approach (Newman et al., 2019), and reduced social approach can be observed in the absence of social vigilance (A. V. Williams & B. C. Trainor, unpublished). A major unanswered question is why social stress does not affect oxytocin neurons in males as it does in females. In adult California mice, gonadal hormones are not a critical mechanism driving sex differences (Trainor et al., 2011, 2013). However, both male and female juvenile California mice exhibit stress-induced social vigilance (E. C. Wright & B. C. Trainor, unpublished). Studies in male adolescent male C57Bl6/J mice show that social stress reduces social approach (Iñiguez et al., 2014, 2016) and increases vigilance (S. Iñiguez, unpublished). Interestingly, populations of "unsusceptible" mice, which do not exhibit decreased social approach, are routinely observed in adult male C57Bl6/J (Bagot et al., 2015; Cao et al., 2010; Krishnan et al., 2007) but have not been reported for adolescent mice. These results implicate adolescence as a key time window during which neural circuits of social vigilance may be reprogramed.

Knowledge of BNST structure and function during adolescent development is sparse. Several subregions of the BNST are larger in males compared with females (Allen & Gorski, 1990; Campi, Jameson, & Trainor, 2013; Morishita, Maejima, & Tsukahara, 2017), and some show sex differences in chemoarchitecture (Bamshad, Novak, & Devries, 1993; Gegenhuber & Tollkuhn, 2019; Juntti et al., 2010). These sex differences in the neuroanatomy likely contribute to sex-dependent reproductive behaviors (Juntti et al., 2010) and learning patterns (Bangasser, Santollo, & Shors, 2005; Bangasser & Shors, 2008). Rodent studies show that post-natal testosterone exposure increases the size of some subregions of BNST (del Abril, Segovia, & Guillamon, 1987) and increases vasopressin production (Han & De Vries, 2003). However, additional sexual differentiation may occur later in life. A study of post-mortem human brain samples showed that sex differences in the size of the BNST were not present in samples from children, but were present in adults (Chung, Vries, & Swaab, 2002). To date, human neuroimaging studies have not examined developmental changes in the BNST. However, cross-sectional studies have reported that during puberty amygdala volumes tend to increase in boys and decrease in girls (Vijayakumar, Op de Macks, Shirtcliff, & Pfeifer, 2018). Cross-sectional studies have not detected associations between gonadal hormones and amygdala volumes, but a longitudinal study showed that boys with greater increases in testosterone during adolescence had larger increases in amygdala volume (Wierenga et al., 2018). In cross-sectional studies, age and testosterone are confounded during adolescence, so longitudinal studies represent a more powerful approach for detecting associations between gonadal hormones and brain development. Changes in amygdala anatomy during puberty correspond with sex differences in functional properties of medial amygdala neurons that emerge during puberty in mice (Bergan, Ben-Shaul, & Dulac, 2014). While there are still significant gaps in knowledge, it appears that adolescence could be a key period for maturation of the BNST and amygdala.

Consistent with this idea, work in mice shows that in both males and females, gonadal hormones modulate the size and chemoarchitecture of the posterior BNST during puberty (Morishita et al., 2017). It is unknown whether any of these sex differences contribute to social vigilance or anxiety. Work in rats suggests that the BNST seems to be more reactive to social contexts during adolescent development than in adulthood (Saalfield & Spear, 2019), at least in males. For example, interacting with an unfamiliar male generated stronger c-fos responses in the BNST and central nucleus of the amygdala in adolescent male rats compared with adult male rats (Varlinskaya, Vogt, & Spear, 2013). The BNST is also responsive to social threats in adolescent monkeys (Fox, Shelton, Oakes, Davidson, & Kalin, 2008), but comparable data on BNST function are not available for adolescent rodents or humans. More data comparing male and female behavior and brain function during adolescence could provide important insights, as emerging data indicate that significant reorganization of neural circuits can occur during this period. For example, major synaptic reorganization has been described in the prefrontal cortex (Delevich, Thomas, & Wilbrecht, 2018).

6 | EXECUTIVE CONTROL OF ANXIETY-RELATED BEHAVIOR

Similar to the BNST, the prefrontal cortex undergoes major changes during adolescent development. Rodent studies show that the number of synapses in the frontal cortex decreases in both males and females during adolescence (Drzewiecki, Willing, & Juraska, 2016), an effect that is accelerated by gonadal hormones in females (Piekarski, Boivin, Boivin, & Wilbrecht, 2017). Fewer synapses may contribute to decreases in gray matter observed during adolescence by human imaging studies (Lenroot & Giedd, 2006; Vijayakumar et al., 2018). The decline in synapse number is associated with an increase in stability among remaining synapses (Pattwell et al., 2016). Changes in synaptic plasticity in the prefrontal cortex could impact anxiety-related behaviors such as social vigilance (Figure 4).

Anatomical tracing studies in rodents show that medial prefrontal cortex has direct connections with the BNST both from its prelimbic (Chiba, Kayahara, & Nakano, 2001; Radley, Gosselink, & Sawchenko, 2009; Room, Russchen, Groenewegen, & Lohman, 1985; Vertes, 2004) and infralimbic regions (Chiba et al., 2001; Hurley, Herbert, Moga, & Saper, 1991; Room et al., 1985; Vertes, 2004). Emerging data

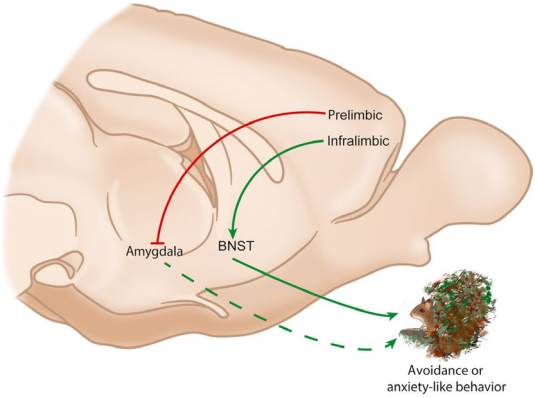

FIGURE 4 Simplified model for interactions between the frontal cortex and bed nucleus of the stria terminalis (BNST). Excitatory neurons in the infralimbic cortex project to the BNST, which plays an important role in driving anxiety-related behaviors. In contrast, the prelimbic cortex exerts inhibitory input on the amygdala, which in turn may reduce anxiety-related behaviors. Mouse drawings by Natalia Duque-Wilckens

suggest that the more dorsal prelimbic cortex and the more ventral infralimbic cortex have distinct effects on behavioral responses to threat (Calhoon & Tye, 2015). When mice explore anxiogenic environments such as the open arms of an elevated plus maze, neural activity within the ventral prelimbic cortex increases (Adhikari, Topiwala, & Gordon, 2010, 2011). These neurons receive input from the ventral hippocampal neurons, and optogenetic inhibition of these inputs increased exploration (Padilla-Coreano et al., 2016). These data are generally consistent with the human imaging studies reporting increased activity in frontal cortex activity in response to aversive contexts. A blind spot in the literature is over-reliance on data from male rodents, even though there is growing evidence that stress-induced plasticity in frontal cortex function can be sex-specific (Baratta et al., 2019; Gruene, Roberts, Thomas, Ronzio, & Shansky, 2015). Interestingly, ventral hippocampus also has strong connections with ventral BNST (Cullinan, Herman, & Watson, 1993), which also can drive anxiogenic states (Jennings et al., 2013). Ventral BNST contains oxytocin neurons that become more reactive in females following social defeat (Steinman et al., 2016). Suppression of oxytocin synthesis in the ventral BNST also reduces stress-induced vigilance in females (N. Duque-Wilkens & B. C. Trainor, unpublished), suggesting that ventral BNST is an important node for anxiety-related behaviors in social contexts. Overall, these findings suggest that a circuit encompassing the ventral hippocampus, prelimbic cortex and ventral BNST is important for generating anxiety-related behaviors in threatening contexts. As mentioned above, the BNST also receives input from the infralimbic cortex. Interestingly, several lines of evidence suggest infralimbic cortex reduces behavioral responses to threat. For example, increased activity in the infralimbic cortex is important for the extinction of conditioned fear responses (Chang, Berke, & Maren, 2010; Holmes et al., 2012; Milad & Quirk, 2002). Infralimbic cortex has strong functional connections with amygdala (Kim, Gee, Loucks, Davis, & Whalen, 2011), and these projections are essential for effective extinction of fear responses (Bloodgood, Sugam, Holmes, & Kash, 2018; Sierra-Mercado, Padilla-Coreano, & Quirk, 2011). Currently, the functional effects of infralimbic projections to BNST have not been examined, so further study of the impact of anxiety or threat on neural activity within the frontal cortex is needed (Park & Moghaddam, 2017). This is especially true for understanding frontal cortex function in humans.

Human imaging studies have reported contrasting results regarding the relationship between responses of the prefrontal cortex and vigilance to threat. One line of evidence linked increased vigilance and anxiety to reduced activity in lateral or medial prefrontal cortex (Bishop, 2009; Bishop, Duncan, Brett, & Lawrence, 2004). Among children diagnosed with anxiety disorders, individuals reacting more quickly to aversive images had reduced functional connectivity between medial prefrontal cortex and amygdala (Price et al., 2016). Reduced functional connectivity between medial prefrontal cortex and amygdala while viewing aversive images was also observed in youth who had experienced maternal deprivation (Gee et al., 2013), which is associated with increased anxiety. In contrast, children rated higher for behavioral inhibition (Fu, Taber-Thomas, & Pérez-Edgar, 2017) or trait anxiety (Telzer et al., 2008) had higher levels of activity in the dorsolateral prefrontal cortex (but not mediolateral prefrontal cortex) in tasks that require attention orienting away from aversive images. Transcranial direct current stimulation directed toward dorsolateral prefrontal cortex reduced vigilance toward aversive images in healthy volunteers (Ironside, O'Shea, Cowen, & Harmer, 2016). Similarly, adults diagnosed with post-traumatic stress disorder showed increased activity in ventrolateral prefrontal cortex in response to aversive images (Adenauer et al., 2010). One problem for resolving these apparently contrasting results is that some studies do not report imaging results from all subregions of the prefrontal cortex (dorsomedial, ventrolateral, etc.). This makes it more difficult to assess subregion-specific responses during vigilance, as well as compare with rodent studies that distinguish between infralimbic and prelimbic cortex. A related question is whether the social environment modulates how the frontal cortex regulates vigilance and other anxiety-related behaviors.

Curiously, there is a strong increase in activity in prelimbic cortex of a subordinate male mouse when a dominant is removed (Wang et al., 2011). Experimental enhancement of excitatory neurotransmission in subordinate male mice increased aggressive behavior. This suggests that disruptions in the social environment may be anxiogenic, even when an individual has an opportunity

to compete for higher social status and suggests that the prefrontal cortex regulation of vigilance behavior could be dependent on the social status of the individual. Imaging data from humans also implicate a role for prelimbic cortex in social contexts, as a meta-analysis showed that dorsomedial (prelimbic) prefrontal cortex was consistently linked with adolescent decision-making in social contexts (van Hoorn, Shablack, Lindquist, & Telzer, 2019). These findings highlight another gap in the preclinical literature, the sparse knowledge of how prelimbic or infralimbic cortex affects anxiety-related behavior during adolescence. Adolescence is a time when individuals start to establish themselves as a competitive member of a social group. This is met with a large range of behavioral changes as well as functional and anatomical changes within the frontal cortex (Drzewiecki et al., 2016; Piekarski, Johnson, et al., 2017), yet only a few studies have considered how these changes affect behavior (Pattwell et al., 2016). Similarly, there are opportunities to consider how changing social environments affect prefrontal cortex in females, as recent data show that social hierarchies can be studied in female mice housed in more naturalistic conditions (Williamson, Klein, et al., 2019).

The data discussed give some insight into potential pathways for vigilance activation but shed very little light on how vigilance could be suppressed in inappropriate contexts. This is an area ripe for future research, and at this time, the authors have no knowledge of research into executive inhibition of BNST. Future animal studies on this topic should also endeavor to include females, because all of the neurophysiological studies reviewed in this section focused on male mice or rats.

7 | CONCLUSIONS

Here, we reviewed evidence for a novel hypothesis that social vigilance could function as a behavioral strategy for improving one's social status. Studies in rodents indicate that stressful social environments can induce social vigilance, which is mediated in part by the BNST. We also reviewed evidence in mice and fish showing that subordinate individuals could detect changes in their social environment within minutes, and respond by engaging the reproductive axis and frontal cortex. These findings suggest that social vigilance may be an important strategy for detecting changes in the social environment. Imaging studies focusing on anxiety disorders in humans have also linked vigilance and avoidance in the dot-probe tasks, but the extent to which these associations apply to more real-world conditions is less clear. Greater implementation of more ethological approaches such as social interaction tasks or ecological momentary assessments to capture naturalistic variation in daily social interactions could be informative. New methods for quantifying the BNST in human imaging studies provide an opportunity to test whether BNST activity tracks social vigilance, as would be predicted from animal models. Adolescence may be an ideal period for interventions aiming to alter behavioral, cognitive, social or neurobiological features of social anxiety given that puberty is a period of dynamic reorganization across these levels.

The science of adolescence is, in itself, in a period of adolescence. The number of research articles on brain function in adolescence accelerated from less than 70 in the year 2000 to more than 700 in 2018. Although we know that adolescence is a period of sexual differentiation, fundamental questions about the mechanisms that contribute to sex differences in social anxiety remain unanswered. Most human neuroimaging studies have been underpowered to assess sex differences. Although some studies incorporate measures of gonadal hormones, few assess hormone levels longitudinally, which is a more effective analytical approach. Mechanistic studies in animal models systems do not fare much better, even after the implementation of "sex as a biological variable" policies in the United States. Only a few groups have rigorously investigated changes in brain structure and function in adolescent males and females. Thus, there is a major gap in the literature addressing the life-history time point when sex differences in anxiety disorders emerge. Another potential barrier to progress is the limited attention to participants' social status and their social mobility (upward or downward). Incorporating measures of participants' current social context or prior social history could be an important approach for accounting for variability in other neuroendocrine and behavioral variables. Gathering more detailed data on the social environment in clinical populations could help leverage new animal models for assessing sex differences in how social stressors impact the brain (Piekarski, Johnson, et al., 2017). So far, most of these approaches have been applied primarily in adults (but see Bourke & Neigh, 2011). Greater integration between human and animal model studies could facilitate the development of more effective strategies for treating social anxiety.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

Emily Wright, Camelia Hostinar and Brian Trainor wrote the manuscript, drafted the figures and edited the manuscript.

DATA AVAILABILITY STATEMENT

No new data have been used.

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