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Dopaminergic associations between behavioral inhibition, executive functioning, and anxiety in development☆

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ABSTRACT

Temperamental Behavioral Inhibition (BI) is a well-documented risk factor for social anxiety in development. However, not all BI children will ultimately demonstrate anxious symptomology. Levels of inhibitory control have been proposed as a possible risk or protective factor for these children, but research remains mixed on whether higher levels of inhibitory control may increase or decrease risk in development. However, the idea of elevated inhibitory control as a risk factor for maladaptation is often considered incongruent with prior conceptions of advantages conferred by proficient inhibitory control. Here, we review theories pertaining to greater inhibitory control as a risk factor for BI children. We also review how individual differences in dopaminergic activity may link BI, executive functioning, and anxiety both concurrently and longitudinally, explaining these nonlinear relations. By way of these associations, we propose a model examining how transactions between these dopamine- modulated domains over time may predict socioemotional adaptation or maladaptation, and discuss how spontaneous eye blink rate may allow for the developmentally-friendly testing of cognitive and socioemotional associations with dopaminergic activity across different forms of experimental design.

Introduction

Behavioral inhibition (BI) is a temperamental profile characterized by patterns of reticence to novelty, particularly in social situations (Kagan, Reznick, & Snidman, 1988; Rubin, Burgess, & Hastings, 2002). Notably, BI is a well-documented individual risk factor for social anxiety in childhood and adolescence (Chronis-Tuscano et al., 2009; Clauss & Blackford, 2012; Hirshfeld et al., 1992). However, not all children with high BI go on to be highly anxious (Degnan & Fox, 2007). Thus, a body of research has examined moderators evident across development that may characterize patterns of multifinality.

Variation in executive functioning is one empirically supported potential moderator of anxiety trajectories. As such, we examine theoretical and empirical work focused on the interactions between BI, executive functions, and adaptive socioemotional development. In this review we will discuss ways in which individual variation in dopaminergic activity explains evident relations between BI, executive functioning, and anxiety, concurrently and through development. We will link BI, executive functioning, and anxiety with other dopaminergic processes, such as reward processing. We will also propose a model detailing transactions between these domains over time, and how these transactions between BI and executive functioning may lead to adaptive or maladaptive socioemotional

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outcomes. Finally, we propose an easily captured and developmentally-appropriate methodology—eye-blink rate—that is well-suited to studying these transactions across the life span.

Variation in executive functioning influences divergences in a number of developmental trajectories, including the emergence of anxiety (Ansari & Derakshan, 2011; Basten, Stelzel, & Fiebach, 2011; Carlson & Wang, 2007; Eggum-Wilkens, Reichenberg, Eisenberg, & Spinard, 2016; Henderson & Wilson, 2017; Henderson, Pine, & Fox, 2015; Kooijmans, Scheres, & Oosterlaan, 2000; Lengua, 2003; Thorell, Bohlin, & Rydell, 2004; Toren et al., 2000; White, McDermott, Degnan, Henderson, & Fox, 2011; Wolfe & Bell, 2014) and is typically seen as an adaptive or protective mechanism in many domains (Barkley, 1997; Carlson & Moses, 2001; Fitzpatrick, McKinnon, Blair, & Willoughby, 2014). Closely tied to the functioning of the prefrontal cortex (PFC; Zelazo, Carlson, & Kesek, 2008), executive functions allow an individual to flexibly respond to stimuli even in the face of a competing prepotent response, supporting goal attainment (Diamond, 2006). The PFC experiences a protracted developmental trajectory, not reaching maturity until well into adolescence (Casey, Tottenham, Liston, & Durston, 2005). As such, adult-like proficiency in executive functioning comes on-line on a "delayed" basis as compared to many other areas of development (Welsh, Pennington, & Groisser, 1991).

This protracted development also leaves the PFC highly susceptible to environmental influences and experiences that may shape functional profiles and patterns of connectivity with other neural regions (Casey et al., 2005; Thompson-Schill, Ramscar, & Chrysikou, 2009). For the purposes of this review we will consider executive functioning through the lens of a three-factor model, dividing the broad umbrella term into the dissociable components of set shifting, working memory/updating, and inhibitory control (Miyake et al., 2000). Despite lexical overlap, inhibitory control is a distinct construct from BI. Throughout this manuscript the executive function construct of interest will be referred to as inhibitory control and the temperamental profile will be referred to as BI. Additionally, we note that these subdomains of EF are not necessarily a unitary construct. High levels of performance in one domain (i.e. set shifting) may not confer high levels of performance in another (i.e. inhibitory control; Blackwell, Chatham, Wiseheart, & Munakata, 2014).

Positive developmental outcomes typically associated with higher levels of executive functioning include increased school readiness (Fitzpatrick et al., 2014) and more sophisticated theory of mind (Carlson & Moses, 2001) relative to peers. Impaired executive functioning is thought to be a transdiagnostic risk factor for a wide variety of clinical diagnoses (Snyder, Miyake, & Hankin, 2015; Zelazo, 2020), including Attention Deficit Hyperactivity Disorder (ADHD; i.e. Barkley, 1997), Obsessive Compulsive Disorder (OCD; i.e. Shin, Lee, Kim, & Kwon, 2014) and bipolar disorder (i.e. Bora, Yucel, & Pantelis, 2009), non-exhaustively.

Increased levels of attention shifting, a skill embedded within the broader category of executive functions, operates as a protective mechanism against internalizing problems (Eggum-Wilkens et al., 2016; Henderson & Wilson, 2017; Henderson et al., 2015; Toren et al., 2000; White et al., 2011). Similar findings have been reported for working memory (Basten, Stelzel, & Fiebach, 2012; Moran, 2016). However, research remains mixed on whether inhibitory control, although also a domain of executive functioning, specifically acts in the same protective fashion.

While a body of work has found an inverse relation between inhibitory control and internalizing symptomatology (Ansari & Derakshan, 2011; Basten et al., 2011; Kooijmans et al., 2000; Lengua, 2003; Wolfe & Bell, 2014), other research has found that increased inhibitory control may actually act as a risk factor for higher levels of internalizing behaviors, specifically in BI children at temperamental risk for anxiety disorders (Carlson & Wang, 2007; Eggum-Wilkens et al., 2016; Henderson & Wilson, 2017; Henderson et al., 2015; Thorell et al., 2004; White et al., 2011). This work suggests that the relation between inhibitory control and internalizing symptoms may be an inverted-U shape rather than linear, and that BI temperament may further modulate these relations. That is, for children higher in BI, higher levels of inhibitory control may relate to greater internalizing symptoms, and the optimal range of inhibitory control for these children may be found at more moderate levels.

The mechanism supporting the idiosyncratic relation between executive functioning and internalizing problems in the context of temperamental risk has yet to be fully elucidated. Here, we suggest that the behavioral hallmarks of BI, variations in executive functioning, and anxiety behaviors are conceptually, and potentially mechanistically, linked by patterns of dopaminergic activity. Furthermore, we put forth the idea that early behavioral differences in BI children linked to patterns of dopamine signaling bi-directionally interact with emerging competencies in executive functioning to influence development in both cognitive and socio-emotional domains, and either exacerbate or mitigate risk of anxious behaviors and psychopathology (Fig. 1).

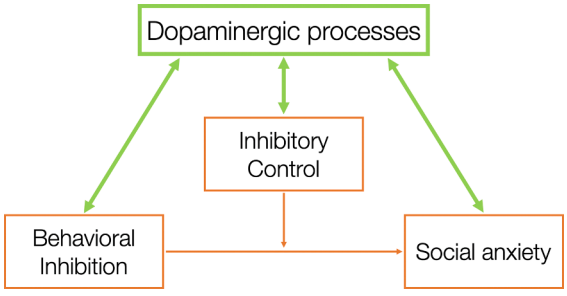

Fig. 1. Conceptual model depicting interactions between BI and inhibitory control on social anxiety, and bidirectional associations between dopamine and each of these processes.

Non-linear impacts of cognitive control in development

Henderson et al. (2015) detail in the Dual Processing Perspective the potential for non-linearity in the relation between inhibitory control and socioemotional maladaptation, specifically in BI children. This approach is rooted in the notion that BI children will more readily implement bottom-up, or stimulus driven, attentional patterns in the face of perceived threat as compared to non-BI peers. An example of this bottom-up process can be seen in the attentional biases to threatening stimuli demonstrated by many BI children (Pérez-Edgar et al., 2010; Roy et al., 2008). Not only do BI children preferentially attend to aspects of the environment that they label as threatening, but they also have a higher propensity to label relatively benign items as threatening (Henderson & Wilson, 2017).

This lack of specificity in orienting also leads to inefficiency, as the child may over-extend and misallocate cognitive resources to stimuli that do not actually signal imminent danger. This indiscriminate focus on threat in turn yields the hypervigilance and reticence that in part characterizes the BI temperamental profile. This hypervigilance and reticence may also be part of the etiology of anxiety disorders, by potentiating negative affect for the individual which may underlie symptoms of anxiety (Lonigan, Vasey, Phillips, & Hazen, 2004). For example, when a BI child enters a room of unfamiliar peers they may label these peers as threats and inappropriately enter a vigilant attentional state (Jarcho & Guyer, 2018). They may then exhibit difficulty in comfortably engaging with the other children, and instead of playing may freeze or remain on the periphery of the scene thus failing to adaptively engage with their social environment (Henderson & Wilson, 2017; Henderson et al., 2015).

This rapid allocation of attention to threat, an automatic process, can call upon controlled processes, like executive functioning, in equal magnitude to help the individual navigate away from a distressing stimulus. The invocation of executive functions, in turn, operates as a positive feedback loop. Higher levels of inhibitory control may aid in the maintenance of attention to threat, which will elicit the continuation of top-down processes, and so on. The role of top-down processes in maintaining rigid socioemotional responses may not be immediately apparent in behavioral data for these children, but are often evident in metrics of neural effort and efficiency (Henderson & Wilson, 2017; Henderson et al., 2015) such as electroencephalography (EEG), event-related potentials (ERPs; Henderson et al., 2015; Henderson & Wilson, 2017; Lahat et al., 2014; Lamm et al., 2014), and functional magnetic resonance imaging (fMRI; Fu, Taber-Thomas, & Pérez-Edgar, 2017).

For example, Fu et al. (2017) found no differences between BI and non-BI children, measured by questionnaire, in behavioral performance on a dot probe attention bias task. In this task, two adjacent faces were presented for 500 ms. The task then measures latency to press a button in response to a probe appearing in the same location as one of the faces. Longer latencies to respond to the probe in a location incongruent with an emotional face is often interpreted as a sign of bias to that emotion. However, the same study found that despite a lack of significant differences in behavior, children high in BI showed greater activation in the dorsolateral prefrontal cortex (dlPFC) during the task as compared to children low in BI. This suggested that children high in BI were recruiting the executive attention network more than their non-BI counterparts during the task in order to perform at a comparable level behaviorally.

Examining more specific executive functioning behaviors, attention shifting may impact how readily BI children can orient attention elsewhere after attending to a threatening stimulus, thus hypothesizing a negative association between anxiety risk and attention shifting (Henderson & Wilson, 2017; Henderson et al., 2015). Based on the Dual Processing Perspective, better attention shifting increases the ease by which children can toggle between automatic and controlled processes, helping to better maintain a balance between these two attentional states (Henderson & Wilson, 2017; Henderson et al., 2015). The ability to visually and attentionally navigate away from a threatening stimulus may mitigate anxiety risk by allowing an individual to continue flexibly engaging with their environment rather than perseverating upon something negative (Henderson & Wilson, 2017; Henderson et al., 2015).

Greater anxiety has also been associated with decrements in working memory, although different theoretical perspectives offer different hypotheses in terms of directionality (Moran, 2016). Some work suggests that increased levels of worry and rumination that is associated with higher levels of anxiety may interfere and compete with the level of attention to be allocated to a working memory task, thus yielding impairments in behavioral performance (Eysenck, Derakshan, Santos, & Calvo, 2007; Moran, 2016). Other work posits that degraded working memory makes an individual more susceptible to distractors in their environment, so an individual with lower working memory abilities has a diminished ability to suppress negative/intrusive thoughts. This may yield heightened negative affect and thus a heightened anxiety risk (Brewin & Smart, 2005; Lonigan et al., 2004; Moran, 2016)

However, Henderson et al. (2015) and Henderson and Wilson (2017) suggest that increased levels of inhibitory control, in contrast, may increase attention allocation to threat in BI children by supporting behavioral rigidity, making it more difficult for a child to switch between automatic and controlled processes, and thus working in opposition to attention shifting. Therefore, inefficiency in shifting from a state of automatic processing to a state of controlled processing may in turn contribute to the development of anxious symptomatology by potentiating attention biases to threatening stimuli, as well as prolonging hypervigilance and negative affect (Henderson & Wilson, 2017; Henderson et al., 2015). After the initial capture of attention by potential threat, it is the balance of attention shifting and inhibitory control that may render a child either able to navigate their attention away from the stimulus and continue exploring their environment, or leave them fixated upon the stimulus and unable to continue engaging with their social world.

Overall, the Dual Processing Perspective broadly suggests that heightened automatic processing, as sometimes found at high levels of BI, can trigger processes associated with executive functioning. However, higher levels of executive functioning, specifically inhibitory control, do not universally predict lower levels of anxiety (Henderson & Wilson, 2017; Henderson et al., 2015). This argument may be inconsistent with many conventional conceptualizations of executive functioning, as reviewed above. However, a body of empirical work supports the notion that more is not always better. Experimentally, Carlson and Wang (2007) found that higher

levels of inhibitory control did not universally predict greater competencies in emotion regulation. In a sample of preschool children, performance on a battery of both inhibitory control and emotion regulation tasks were significantly correlated, but as an inverted-U shape rather than linearly. Medium levels of inhibitory control predicted the highest level of emotion regulation, with both the lowest and highest levels of inhibitory control predicting lower emotion regulation ability (Carlson & Wang, 2007). Low levels of emotion regulation may be a risk factor for anxiety disorders (Amstadter, 2008; Suveg & Zeman, 2004).

White et al. (2011) found similar associations between inhibitory control and anxiety symptoms in a sample of 4-year-olds assessed for level of BI in the laboratory as toddlers. Amongst children high in BI as toddlers, those with high levels of attention shifting as measured by the dimensional change card sort task reported lower anxiety symptoms via questionnaire. Conversely, for children high in BI as toddlers, those with high levels of inhibitory control as measured by a Stroop task reported *greater* anxiety symptoms. The authors proposed that the potentiating effects of inhibitory control in BI children could be associated with a lack of adaptability in one's behavior across changing contexts.

High levels of inhibitory control may contribute to inflexible and rigid behaviors, especially in emotional, social, or threat-related situations, and thus increased perseverance on these cues. For example, recent work suggests that rigid patterns of attention across tasks (Morales, Taber-Thomas, & Pérez-Edgar, 2017) and contexts (Fu, Nelson, Borge, Buss, & Pérez-Edgar, 2019), is associated with greater anxiety risk among BI children, concurrently. The continuation of these biases over time may develop into increased anxiety symptomatology for these children. On the other hand increased levels of attention shifting may yield higher levels of behavioral flexibility and thus help to ameliorate these temperamental or behavioral predispositions for anxiety (White et al., 2011). The amount of time spent attending to a perceived threat and in a hypervigilant state relates to anxious symptomatology (Henderson & Wilson, 2017). Thus, behaviors that help to break these biases and minimize non-goal directed, non-restful time when there is indeed no threat would be the most adaptive.

Thompson-Schill et al. (2009) also suggest that hypofrontality, or an immature PFC, supports adaptive development. This approach suggests that the protracted development of the PFC, and accompanying developmental periods of behavioral and cognitive under-control, may contribute to higher rates of learning through childhood. Where lower levels of cognitive control may relate to under-performance in some domains, such as Stroop tasks, the authors suggest that in the long run lower levels of cognitive control may also enable a child to more effectively learn and update rules about their world. Within this framework, overly heightened control may be to the detriment of these normative learning processes because it precludes the ability to maximally interact with the environment (Thompson-Schill et al., 2009).

The dual processing and hypofrontality perspectives fit into larger frameworks of development suggesting that the extremes of a neural mechanism may not be optimal for adaptive development, and moderate levels may be more favorable (Northoff & Tumati, 2019). A traditional way of statistically analyzing differences between typical and atypical development centers on group comparisons, which limits our approach to linear modeling (Northoff & Tumati, 2019). However, non-linear analyses often reveal that neither low- nor high-extremes of biological processes are adaptive for development, and indeed an inverted "U" shape may best describe the association between biological mechanisms and optimal functioning (Northoff & Tumati, 2019).

Within the domain of executive functioning, classic work suggests that "more is good" in predicting favorable development (Barkley, 1997; Basten et al., 2012; Carlson & Moses, 2001; Eggum-Wilkens et al., 2016; Fitzpatrick et al., 2014; Henderson et al., 2015; Henderson & Wilson, 2017; Moran, 2016; Toren et al., 2000; White et al., 2011). However, both the dual processing perspective and hypofrontality suggest that while low levels of attention shifting, inhibitory control, and/or working memory may be deleterious, high levels of the same behaviors may also be equally detrimental for adaptive functioning. Mixed findings regarding the benefits associated with high and low levels of executive functioning may arise from differences in modeling or sampling (Northoff & Tumati, 2019). For example, assuming linearity rather than testing nonlinear models may yield different results (Northoff & Tumati, 2019). Another opportunity for differences in findings to emerge is in sampling scheme. Sampling levels of a behavior either as a binary variable or at frequencies along a bell curve may yield different findings than oversampling at extremes, for example (Northoff & Tumati, 2019).

Measuring dopaminergic activity to capture mechanisms of executive functioning

As reviewed, the relation between socioemotional adaptation and executive functioning is not necessarily straightforward. We propose that capturing patterns of dopamine signaling throughout development may better elucidate these relations and their underlying mechanisms.

Dopaminergic activity as a neural correlate of executive functioning

Dopamine is a neurotransmitter associated with a wide spectrum of social and nonsocial behaviors, as well as clinical diagnoses ranging from Parkinson's disease to Schizophrenia (Hornykiewicz, 1966). Dopamine receptors can be of five different subtypes (D1, D2, D3, D4, and D5) and are expressed widely throughout the brain, contributing to the diversity of associated domains (Ayano, 2016).

Dopamine and dopaminergic receptors are broadly associated with the planning, goal-direction, memory, and inhibition processes that are key features of executive functioning (Ayano, 2016; Diamond, 2006), although the directionality of these associations is mixed across studies. Prior work has found positive linear relations between executive functioning and binding to D1 receptors in the striatum (Karlsson et al., 2011), D2 and D3 receptors in the anterior cingulate cortex (ACC; Lumme, Aalto, Ilonon, Någren, & Hietala, 2007), and D2 receptor binding in the hippocampus (Takahashi et al., 2008). McNab et al. (2009) found an inverse relation between binding potential in cortical D1 receptors and working memory performance. Takahashi et al. (2008) found an inverted-U relation between D1

receptor binding in the PFC and performance on the Wisconsin Card Sorting task, a common executive functioning assessment.

However, dopaminergic activity is difficult to measure directly and non-invasively in human models because current common neuroimaging techniques do not reliably index neurochemical changes (Badgaiyan, 2014). In humans, eye blink rate is regarded as a promising peripheral, non-invasive index of striatal dopamine activity (Jongkees & Colzato, 2016; Karson, 1983; Van Slooten, Jahfari, & Theeuwes, 2019), specifically linked to striatal D1 and D2 receptors (Jongkees & Colzato, 2016), which are in turn broadly related to both cognitive and emotional control (Ayano, 2016). Early work noted that individuals with Parkinson's Disease, a neurological disorder characterized in part by low levels of dopaminergic activity, have lower rates of spontaneous eye blinks (Hall, 1945), which then led to experimental investigations of this association. For example, the administration of dopamine agonists is significantly related to increased spontaneous eye blink rate in monkeys (Karson, 1983). In humans, similar pharmacological manipulations yield generally comparable findings (Jongkees & Colzato, 2016). Looking to other special populations beyond individuals diagnosed with Parkinson's disease, a number of studies also show that individuals with schizophrenia, characterized in part by high levels of dopaminergic activity in the striatum, show increased spontaneous eye blink rates (Jongkees & Colzato, 2016).

Despite strong correlations between clinical and pharmaceutical manipulations of dopamine binding patterns, the exact mechanism linking dopamine and eye blink rate remains unclear (Bacher & Smotherman, 2003). However, there is evidence that this association between eye blink rate and dopaminergic activity persists through the lifespan and is evident as early as infancy (Bacher & Smotherman, 2003). In addition, variables influencing rate of eye blink remain relatively constant through development (Bacher & Smotherman, 2003). These findings provide support for using eye blink rate as a proxy for dopaminergic activity throughout development (Bacher & Smotherman, 2003).

Prior work shows that spontaneous eye blink rate is associated with executive functions amongst healthy adults (Colzato, van den Wildenberg, van Wouwe, Pannebakker, & Hommel, 2009; Zhang et al., 2015). Work by Zhang et al. (2015) suggests a positive relation between spontaneous eye blink rate and accuracy on an attention shifting task, as well as an inverse relation between eye blink rate and shifting cost on the same task. These findings suggest a positive relation between dopaminergic activity and attention shifting (Zhang et al., 2015). Conversely, in the same sample, Zhang et al. (2015) found an inverse relation between spontaneous eye blink rate and performance on an updating/working memory task, suggesting that higher levels of dopamine may actually degrade working memory ability (Zhang et al., 2015).

Findings remain less consistent for associations between dopamine and inhibitory control. Zhang et al. (2015) found that higher spontaneous eye blink rate was positively related to accuracy on a go/no go task and lower inhibition cost on a Stroop task, suggesting a positive relation between dopamine levels and inhibitory control proficiency. But, conversely, Colzato et al. (2009) found evidence of an inverse relation between dopamine levels and inhibitory control proficiency, wherein eye blink rate was related to slower reaction times on a stop signal task, a marker of less efficient inhibitory control. The varying relations between striatal dopamine levels and different sub-behaviors encompassed by executive functions, especially within the same sample (Zhang et al., 2015), suggest that dopamine may play a different role in the execution and efficiency of each sub-domain of behaviors and that the relation between dopamine and executive functioning may be nonlinear (Colzato et al., 2009; Zhang et al., 2015).

Nonlinear relations between levels of dopamine binding and behavior

As described above, there are both non-positive and nonlinear relations between executive functioning and adaptive socioemotional development specifically in BI children. The inverted-U pattern seen in associations between executive functioning and metrics like anxiety risk is mirrored in evident relations between dopamine neurotransmission and executive functioning. Based on their morphology, D1 receptors are excitatory and D2 receptors are inhibitory (D5 receptors are considered "D1-like" and therefore also excitatory, while D3 and D4 receptors are considered "D2-like" and therefore also inhibitory; Ayano, 2016). The binding of dopamine molecules to D1 receptors is related to "go" behaviors, while binding to D2 receptors is related to suppression or "no go" behaviors (Jongkees & Colzato, 2016). This balance between behaviors suggests an inverted-U trajectory for the adaptiveness of dopamine levels in terms of cognitive function, so greater dopamine binding is not universally advantageous (Jongkees & Colzato, 2016).

For example, high levels of dopamine may simultaneously activate go tendencies and suppress no go tendencies, lowering the threshold for initiating behavior (Jongkees & Colzato, 2016). On the other hand, low levels of dopamine will fail to activate go tendencies and fail to suppress no go tendencies, so there is a higher threshold for initiating behavior and the individual may appear to be more inhibited (Jongkees & Colzato, 2016). While high levels of inhibition may be clearly disadvantageous, rendering an individual inflexible and with minimal environmental engagement and learning, completely uninhibited behavior may be just as deleterious as the individual may lack the control to focus attention and behavior adequately for goal attainment (Jongkees & Colzato, 2016).

Dopaminergic activity as a neural correlate of anxious behaviors

Dopaminergic activity is associated with mood and emotion regulation as well as reward processing (Ayano, 2016), all of which are implicated in the etiology of anxiety disorders (Amstadter, 2008; Silk, Davis, McMakin, Dahl, & Forbes, 2012). The amygdala is populated with inhibitory D4 dopamine receptors (Ayano, 2016) and is involved in anxiety-like behavior (Zarrindast & Khakpai, 2015). For anxious individuals, amygdala hyperactivation mirrors mis- and over-classification cues of danger versus safety (Britton, Lissek, Grillon, Norcross, & Pine, 2011). Amygdala activity is also modulated by the PFC, another area rich with dopaminergic activity, wherein the PFC can downregulate amygdala activity to provide greater specificity in responding to negative and threat-related cues (Britton et al., 2011; Pérez de la Mora, Gallegos-Cari, Arizmendi-Garcia, Marcellino, & Fuxe, 2010). Reward processing and reinforcement learning are also generally associated with the amygdala, as well as with other midbrain structures including the striatum

(Caouette & Guyer, 2014), which are populated with dopamine receptors as well (Ayano, 2016; Caouette & Guyer, 2014).

Experimentally, patterns of binding to dopamine receptors show an inverse relation with anxiety symptomatology (Cervenka et al., 2012; Moraga-Amaro, Gonzalez, Pacheco, & Stehberg, 2014). Broadly, dopamine depletion may be associated with anxiety-like behaviors, evidenced by work in both rodents and humans (Zarrindast & Khakpai, 2015). In mouse models, low counts of systemic dopamine D3 receptors have been associated with increased anxiety-like behaviors (Moraga-Amaro et al., 2014). In human models, increased binding potential to D2 receptors in the medial prefrontal cortex (mPFC) and hippocampus as measured with positron emission tomography (PET) has been associated with decreases in reported social anxiety symptoms after treatment with cognitive behavioral therapy (Cervenka et al., 2012). In addition, specific polymorphisms of genes associated with dopamine signaling, including DRD4, MAO-A, and COMT, are associated with both anxious behaviors and clinical diagnoses of anxiety disorders (i.e. Pérez-Edgar et al., 2014; Samochowiec et al., 2004; Stein, Fallin, Schork, & Gelernter, 2005), further suggesting a link between dopaminergic activity and anxiety risk.

Differences in reward processing as a hallmark of behavioral inhibition and anxiety

The BI phenotype includes behaviors that comprise adaptive socioemotional engagement and functioning, such as biased attention to threat and social withdrawal (Chronis-Tuscano et al., 2009; Hirshfeld et al., 1992; Kagan et al., 1988; Lonigan et al., 2004). Prior work also suggests that BI children may process rewards differently than non-BI children (Guyer et al., 2006, 2012), a set of behaviors also associated with dopamine signaling (Cremers, Veer, Spinhoven, Rombouts, & Roelofs, 2015; Guyer et al., 2006, 2012; Richey et al., 2014). Differences in reward processing between BI and non-BI children may underlie divergence in the way they interface with and learn about their environment (Britton et al., 2011; Mkrtchian, Aylward, Dayan, Rosier, & Robinson, 2017).

BI and socially phobic adolescents show patterns of hyperactivation in the striatum to increasing incentives in a monetary incentive delay task, in the absence of significant differences in behavior. These findings suggest a heightened neural sensitivity to reward amongst BI and socially phobic individuals as compared to their control counterparts (Guyer et al., 2006, 2012). However, adolescents with a diagnosis of generalized anxiety disorder do not show these patterns (Guyer et al., 2012), suggesting some specificity of this hyperactive reward sensitivity to anxiety profiles particularly sensitive to social contexts and thus possibilities of downstream impacts on social behavior specifically.

In examining sensitivity to social rewards amongst socially anxious individuals during a Social Incentive Delay task, individuals with social anxiety disorder showed heightened patterns of striatal activity in response to avoiding punishment as compared to gaining a reward (Cremers et al., 2015). In another sample, socially anxious adults demonstrated hypoactivation in the nucleus accumbens, part of the striatum, in anticipation of social reward, but showed hyperactivation in the nucleus accumbens in anticipation of monetary reward (Richey et al., 2014). These differences in neural sensitivity to social and non-social rewards and punishments fundamentally change the aspects of the environment that an individual will approach and avoid in their social world as a function of what they find to be rewarding. In this case, an individual with social anxiety may find a putative social reward to be less rewarding, and may therefore be less likely to approach the person or event (Richey et al., 2014). These interactions in turn shape subsequent learning about social stimuli (Mkrtchian et al., 2017). Patterns of learning regarding one's social world then informs the proficiency with which one approaches social interactions, and these "successes" or lack thereof may have downstream consequences for social adaptation or maladaptation, respectively.

Reinforcement learning

Learning is a critical developmental process that dynamically shapes experience-dependent neural connections through the lifespan (Johnson, 2001). Midbrain structures such as the amygdala and striatum are functionally linked to the PFC and are related in processes linked with reinforcement learning, such as reward valuation (Britton et al., 2011; Caouette & Guyer, 2014; Costa, Dal Monte, Lucas, Murray, & Averbeck, 2016). Furthermore, dopaminergic activity in these regions has been documented as a key role in reinforcement learning, supported though a number of multimodal investigations. Experimentally, the administration of a D2/D3 receptor agonist, which limits bursts of dopaminergic activity, degrades learning during a probabilistic reward task (Santesso et al., 2009). Looking to peripheral measures of dopaminergic activity, low spontaneous eye blink rate (suggesting lower striatal dopamine levels) was associated with a higher rate of learning from negative outcomes specifically during a reinforcement learning task (Slagter, Georgopoulou, & Frank, 2015).

Reinforcement learning pertaining to threatening stimuli is heavily implicated in anxiety disorders in that anxious individuals may have disproportionately negative responses to benign stimuli (Britton et al., 2011). In navigating their environment, both anxious individuals and BI individuals are identified by patterns of behavioral avoidance of identified threats during reinforcement learning paradigms (Mkrtchian et al., 2017). This avoidance of negative consequences is also associated with enhanced error monitoring, which is frequently operationalized by a larger negative deflection of the error-related negativity (ERN) event related potential (ERP) amplitude, measured by electroencephalography (EEG), after an erroneous task response (Frank, Woroch, & Curan, 2005; Holroyd & Coles, 2002; Mkrtchian et al., 2017). The ERN is also related to dopamine activity, such that the negative deflection is related to decreases in dopamine levels in the anterior cingulate cortex after an error is made (Frank et al., 2005; Holroyd & Coles, 2002). Tasks to elicit neural signatures of error monitoring include the Flanker task, focusing on trials in which an incorrect response was given by the participant (Lahat et al., 2014). Prior work has also marked exaggerations in this neural signature as a risk factor for anxiety, specifically amongst BI children (Lahat at al., 2014; McDermott et al., 2009).

A way of mitigating this biased behavior is through experiencing and learning about the consequences of interacting with

potentially distressing stimuli, ultimately binding a non-punishing outcome with a benign stimulus. However, for an anxious individual operating within a dynamic social world (and outside of a computer task), it is less likely that they will actually approach and learn from a stimulus they have initially labeled as threatening (Mkrtchian et al., 2017). This tendency to avoid the uncertain to mitigate possible penalty may further exacerbate the avoidant tendencies that are already highly evident in both anxious and BI individuals (Kagan et al., 1988; Mkrtchian et al., 2017; Rubin et al., 2002). This avoidance may limit experiential learning to the point of engendering restrictive, maladaptive behaviors and/or psychopathology (Mkrtchian et al., 2017).

Exploration versus exploitation

Exploration can be defined as an individual widely examining their environment for new opportunities that may be highly rewarding (Pérez-Edgar, 2018). Exploitation suggests repeating a more narrow set of behaviors for an opportunity that is more certain and familiar, but perhaps less rewarding than other available, but less reliable, avenues (Pérez-Edgar, 2018). An individual's flexible responses to environmental demands often relies on a repertoire of behaviors that includes an toggling between exploration and exploitation strategies as a function of context, strategically calling upon the top-down control implicated by executive functioning (Diamond, 2006; Pérez-Edgar, 2018).

Interactions with one's environment provide an opportunity for reinforcement learning. As an individual explores their environment, they may associate various outcomes, good or bad, with different stimuli. Individual differences in reinforcement learning may arise from the stimuli that individuals actually interact with through this learning process, or differences in exploration versus exploitation (Britton et al., 2011; Mkrtchian et al., 2017; Pérez-Edgar, 2018). A distinct profile of exploitative over exploratory behaviors in navigating one's environment is another posited characteristic of BI children as well as a risk factor for anxiety disorders (Pérez-Edgar, 2018).

BI children may be less proficient in toggling between exploration and exploitation (Henderson & Wilson, 2017; Henderson et al., 2015). A BI child may opt for a more exploitative strategy, choosing a familiar set of behaviors to minimize novelty and risk while still retaining a high probability of attaining moderate reward (Pérez-Edgar, 2018). This behavior may become highly entrenched and rigid for the child, lacking the ability to adapt across contexts (Henderson & Wilson, 2017; Henderson et al., 2015; Pérez-Edgar, 2018; White et al., 2011). Especially in generally safe and low-risk environments, this narrowing set of behaviors may in turn prove maladaptive for a child navigating their social world, limiting social opportunities and learning, and thus posing increased risk for internalizing difficulties or anxiety (Humphreys et al., 2015; Pérez-Edgar, 2018).

Associations between dopamine signaling and exploratory versus exploitative strategies have been noted in human models using peripheral measures of dopaminergic activity. For example, Van Slooten et al. (2019) had a sample of adults complete a reinforcement learning task while their eye blinks were recorded using a stationary eye tracker. During a learning phase, participants were presented with option pairs (high reward probability versus low reward probability) and learned to choose the more rewarding of the two options. In a subsequent phase, participants were presented with novel arrangements of these different options and were asked to choose which option they wanted based on reward value. The participants' ability to choose the most rewarding option and avoid the least rewarding option was noted across trials. Participants were also categorized as low or high spontaneous eye blink rate.

The authors (Van Slooten et al., 2019) found no significant group differences during the second phase during which the participants freely chose their preferred option. However, individuals with a lower eye blink rate performed better during the learning phase. That is, they were more likely to choose the greater value options during this block of the task. Driving these differences in performance were the strategies that individuals used during the task. The authors found that participants with a lower eye blink rate were more

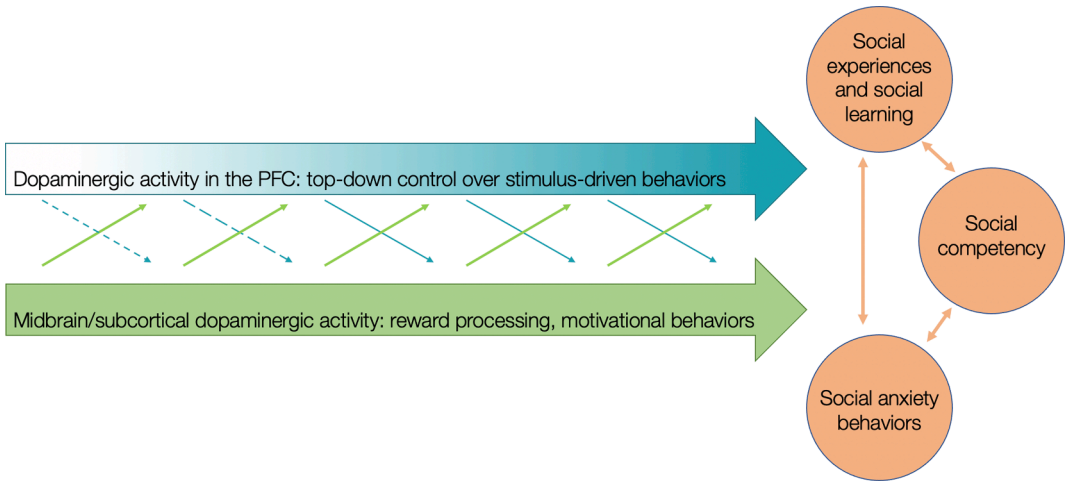

Fig. 2. Conceptual model depicting the influence of behaviors associated with dopaminergic activity in the midbrain and subcortical areas, such as reward processing and motivational behaviors, on social development, and the emerging bidirectional interactions of top-down behaviors such as executive functioning, associated with dopaminergic activity in the prefrontal cortex.

likely to *exploit* higher value options, while participants with a higher eye blink rate were more likely to *explore* lower value options. While the higher eye blink rate participants were less likely to "correctly" choose the higher value options, their tendency to explore the alternate options was considered more flexible and adaptive for exploring the learning environment (Van Slooten et al., 2019).

Learning is a critical component of development, and is as a driving force in the changes seen in both brain and behavior through the lifespan (Johnson, 2001). However, differences in explorational disposition seen between low- and high-risk anxiety individuals have the potential to severely restrict what learning experiences an individual may have. If an individual explores their real-life environment, they may shape interpersonal skills and social competency to in turn learn that novelty is indeed not so threatening. However, without this experience one's social world may remain daunting and unknown, continuing limited, maladaptive interactions with the environment to the point of psychopathology.

Anxiety risk as an ensemble of midbrain and frontocortical dopaminergic activity

Dopamine is a widespread and versatile neurotransmitter, influencing many domains of human behavior (Ayano, 2016). Here, we have focused primarily on the role of dopamine in executive functions primarily implicating the PFC, as well as in reward processing and reinforcement learning, implicating midbrain regions such as the amygdala and striatum. We posit that it is the interaction between these domains of cognition that, over time, shape the anxious phenotype, specifically amongst BI children (Fig. 2).

As reviewed, both BI and anxiety are characterized via an array of dopamine-associated behaviors and neural signatures in reward-related tasks (Britton et al., 2011; Frank et al., 2005; Holroyd & Coles, 2002; Lahat et al., 2014; McDermott et al., 2009; Mkrtchian et al., 2017; Pérez-Edgar, 2018). These behaviors include a broad avoidance of potential losses and a higher propensity to learn from threats during reinforcement learning paradigms (Britton et al., 2011; Mkrtchian et al., 2017), as well as patterns of low exploration and high exploitation (Pérez-Edgar, 2018). Another common motif in these findings is that these behaviors are all associated with low dopamine at binding sites within the midbrain region (Frank et al., 2005; Holroyd & Coles, 2002; Santesso et al., 2009; Slagter et al., 2015; Van Slooten et al., 2019). We suggest that individual differences in levels of dopamine and dopamine binding in the midbrain may restrict the repertoire of goal-directed and reward-driven behaviors that a child may deploy in navigating their environment, from early in development, thus constraining experiences which in turn limit experience-dependent social learning processes.

Also reviewed is the association between dopamine and executive functioning, although the directionality of these associations may be less clear. Increased dopamine measured by eye blink rate may be related to increased levels of attention shifting and decreased levels of working memory (Zhang et al., 2015), as well as mixed associations between dopamine levels and inhibitory control (Colzato et al., 2009; Zhang et al., 2015). This top-down control of behavior is heavily linked to the PFC (Zelazo et al., 2008), another location where dopamine receptors are expressed (Ayano, 2016). The goal-directed behavior shaped by executive functioning and the PFC may help an individual in implementing and flexibly switching between reward-driven behaviors to help guide their actions toward higher-order goals (Henderson & Wilson, 2017; Pérez-Edgar, 2018). These interactions between reward-driven and goal-directed behaviors are supported by structural and functional connections between regions of the cortex, like the PFC, and areas of the midbrain related with reward processing such as the amygdala and the striatum (Ayano, 2016; Britton et al., 2011). This connectivity allows for top-down modulation over more stimulus-driven behaviors (Britton et al., 2011; Henderson & Wilson, 2017; Henderson et al., 2015; Pérez de la Mora et al., 2010).

Reward valuation and cognitive control are each linked to overlapping dopaminergic activity. Executive functioning is instrumental in the effective and adaptive implementation of reward-related behavior and learning. Some individuals may be neurochemically predisposed to a more limited set of adaptive reward-related behaviors by way of differences in dopamine release or dopamine binding (Pérez-Edgar et al., 2014; Schmidt, Fox, Pérez-Edgar, & Hamer, 2009; Schmidt, Fox, Pérez-Edgar, Hu, & Hamer, 2001; Slagter et al., 2015; Van Slooten et al., 2019). Furthermore, a neurochemical profile of lower dopamine activity may underlie many hallmark behaviors of BI and anxiety such as greater exploitation and lower exploration (Van Slooten et al., 2015), a negativity bias in learning (Slagter et al., 2015), differences in error monitoring (Frank et al., 2005; Holroyd & Coles, 2002; Lahat et al., 2014; McDermott et al., 2009), as well as correlate with general anxiety symptomology (Cervenka et al., 2012; Moraga-Amaro et al., 2014; Zarrindast & Khakpai, 2015). Lower dopamine activity may also contribute to differences in executive functioning for these same individuals (Colzato et al., 2009; Schillerstrom, Horton, & Royall, 2005; Zhang et al., 2015).

Additionally, the protracted development of the PFC renders the development of executive functioning susceptible to early life influences and experiences (Casey et al., 2005; Thompson-Schill et al., 2009; Welsh et al., 1991), so early differences in reward behavior and reinforcement learning may contribute to later differences in executive functioning processes, like attention shifting and inhibitory control, as well as their neural underpinnings (Johnson, 2001). These differences in flexibility may lead to the entrenchment of maladaptive social repertoires, limiting experiences and thus putting these children at increasing risk for anxiety through development to the point of psychopathology (Henderson & Wilson, 2017; Henderson et al., 2015; Pérez-Edgar, 2018).

Future directions

As reviewed, dopaminergic activity plays a mechanistic link in understanding the origin and potentiation of behaviors that may contribute to anxious symptomatology through development. Behaviors linked to dopaminergic activity, such as exploration and reward processing, strongly influence the way in which a child navigates, and in turn learns about, their social world. These processes, especially early in life, have the ability to shape continued interactions in either an adaptive or maladaptive fashion. Future work should seek to examine neural and behavioral markers of both reward and executive functioning processes concurrently, intra-individual change in these markers over time to better understand their emergence, as well as how these processes may interact

longitudinally in relation to socioemotional outcomes.

Naturalistic paradigms assessing social reward and executive functioning

A shortcoming in the literature assessing cognitive constructs like exploration versus exploitation and accompanying learning tasks is that paradigms are often non-social in nature. Tasks are often incentivized by monetary rewards and stimuli in these games are frequently non-social, such as geometric shapes (i.e. Gonzalez, Allen, & Coan, 2016; Van Slooten et al., 2019). However, it may be critical to emphasize social aspects and contexts of executive functioning when focused on examining how cognition relates to socioemotional development and risk for socioemotional maladaptation. Social stimuli may cue to both positive or negative outcomes, in addition to being inherently rewarding or punitive.

To expand upon the literature on social reward and close this gap, authors such as Britton et al. (2011) have proposed more social paradigms to test fear learning, such as morphing emotion (e.g., angry to happy) between two faces to test generalization of a social stimulus. To better understand social reward processing, other authors have adapted the commonly-used monetary incentive delay task to be social in nature, utilizing positively and negatively emotionally valenced faces rather than monetary values (Cremers et al., 2015; Richey et al., 2014). However, the practice of measuring these constructs nearly exclusively on a computer screen may limit ecological validity.

Computerized tasks offer excellent experimental control and precision, but may not closely mirror "real world" social scenarios. In the "real world," social stimuli are dynamic and mutually responsive, as well as embedded in a complex world with competing motivations and goals. However, social stimuli used in psychological computerized tasks are often static and disembodied faces lacking social context. Thus, computer tasks impose a barrier to engagement between the stimuli and the participant (Risko, Richardson, & Kingstone, 2016). The movement and responsivity of "real life" facial stimuli may be even more critical to consider in the context of BI and social anxiety, since both are in part identified by sensitivity to social and affective stimuli (Fu & Pérez-Edgar, 2019). Furthermore, computer tasks also minimize human motion. While this helps to minimize noise and motion artifacts in many forms of behavioral and physiological data collection, it may also interfere with more naturalistic processes of cognition as processes such as embodied cognition are limited if not halted (Ladouce, Donaldson, Dudchenko, & Ietswaart, 2017).

Indeed, a body of work suggests that findings from ecologically valid paradigms need not closely mirror findings from their more lab-controlled counterparts. In the domain of visual attention, for example, Fu et al. (2019) found that in a live social interaction with a stranger, BI and non-BI children were differentiated by number of gaze shifts toward a stranger where BI children made fewer attentional shifts to a naturalistic social threat than non-BI children. However, when the same children completed the dot probe task on a computer using static emotionally valenced faces, biased attention to faces in this task did not differentiate between the BI and non-BI groups (Fu et al., 2019). Where visual attention is closely related to executive functioning (Amso & Scerif, 2015), these discrepancies speak to the value of implementing ecologically valid paradigms to better understand how cognition may unfold naturalistically and furthermore how individual differences in these measures may modulate risk for socioemotional maladaptation.

Advances in technology have opened many new avenues for ambulatory data collection. While challenges persist in managing signal to noise ratio during many naturalistic paradigms, devices such as ambulatory eye trackers and portable EEG equipment have gained traction in the developmental literature and beyond (Ladouce et al., 2017). These wearable methods of data collection allow for individuals to participate in more true-to-life paradigms designed to target a construct, such as inhibitory control, while measures such as visual attention or neural activity are simultaneously collected. These methods may hold the key to understanding how dopaminergic activity influences social and cognitive behavior in more naturalistic settings. For example, ambulatory eye tracking can be used to measure spontaneous eye blink rate during a naturalistic inhibitory control task akin to how spontaneous eye blink rate may be measured with a stationary eye tracker during a computerized inhibitory control task (Jongkees & Colzato, 2016; Van Slooten et al., 2019).

Breadth of sampling

Mixed findings in the literature regarding the relations between executive functioning and socioemotional development may arise from differences in sampling and analytic approaches, as reviewed. Future directions should consider recruiting participants that represent broader distributions of a behavioral or neural signature and oversampling to include both high and low extremes. This approach allows for the testing of non-linear associations between executive functioning and socioemotional development (Northoff & Tumati, 2019). A focus on distribuition also implicates utilizing behavioral or neural predictors/profiles as continuous rather than categorical variables to allow for the direct examination of the optimal level of a signature for adaptive development and how this "sweet spot" may vary as a function of individual differences (Northoff & Tumati, 2019). Additionally, sample sizes should also be large enough to allow for adequately-powered analyses using nonlinear models (Northoff & Tumati, 2019).

This review summarizes current findings in work linking BI, anxiety, and EF. We also discuss how both dopamine and dopamine-mediated behaviors, such as reward sensitivity, social exploration, and top-down control, may further explain interrelations between these behaviors. Further examining these relations may help elucidate mechanisms underlying potentially idiosyncratic directionalities between BI, anxiety, and EF found in prior work. To test this model empirically, work should further examine nonlinear associations between executive functioning and anxiety in BI children. This work should utilize naturalistic social paradigms and ambulatory data collection to capture the complexities of motivation, emotion, executive functioning, and peripheral measures of dopamine signaling to examine how these related processes may interact in ecologically valid settings. These assessments should also include diverse and broadly sampled populations to both accurately and representatively characterize pathways of risk and resilience

for child socioemotional development.

CRediT authorship contribution statement

Kelley E. Gunther: Conceptualization, Writing - original draft. **Koraly Pérez-Edgar:** Writing - review & editing.

References

Amso, D., & Scerif, G. (2015). The attentive brain: Insights from developmental cognitive neuroscience. *Nature Reviews Neuroscience, 16*(10), 606–619. https://doi.org/10.1038/nrn4025

Amstadter, A. (2008). Emotion regulation and anxiety disorders. *Journal of Anxiety Disorders, 22*(2), 211–221. https://doi.org/10.1016/j.anxdis.2007.02.004

Ansari, T. L., & Derakshan, N. (2011). The neural correlates of impaired inhibitory control in anxiety. *Neuropsychologia, 49*, 1146–1153. https://doi.org/10.1016/j.neuropsychologia.2011.01.019

Ayano, G. (2016). Dopamine: Receptors, functions, synthesis, pathways, locations and mental disorders: Review of literatures. *Journal of Mental Disorders and Treatment, 2*(2), 1–4. https://doi.org/10.4172/2471-271X.1000120

Bacher, L. F., & Smotherman, W. P. (2003). Spontaneous eye blinking in human infants: A review. *Developmental Psychobiology, 44*(2), 95–102. https://doi.org/10.1002/dev.10162

Badgaiyan, R. D. (2014). Imaging dopamine neurotransmission in live human brain. *Progress in Brain Research, 211*, 165–182. https://doi.org/10.1016/B978-0-444-63425-2.00007-6

Barkley, R. A. (1997). Behavioral inhibition, sustained attention, and executive functions: Constructing a unifying theory of ADHD. *Psychological Bulletin, 121*(1), 65–94. https://doi.org/10.1037/0033-2909.121.1.65

Basten, U., Stelzel, C., & Fiebach, C. J. (2011). Trait anxiety modulates the neural efficiency of inhibitory control. *Journal of Cognitive Neuroscience, 23*(10), 3132–3145.

Basten, U., Stelzel, C., & Fiebach, C. J. (2012). Trait anxiety and the neural efficiency of manipulation in working memory. *Cognitive, Affective, and Behavioral Neuroscience, 12*, 571–588. https://doi.org/10.3758/s13415-012-0100-3

Blackwell, K. A., Chatham, C. H., Wiseheart, M., & Munakata, Y. (2014). A developmental window into trade-offs in executive function: The case of task switching versus response inhibition in 6-year-olds. *Neuropsychologia, 62*, 356–364. https://doi.org/10.1016/j.neuropsychologia.2014.04.016

Bora, E., Yucel, M., & Pantelis, C. (2009). Cognitive endophenotypes of bipolar disorder: A meta-analysis of neuropsychological deficits in euthymic patients and their first-degree relatives. *Journal of Affective Disorders, 113*(1–2), 1–20. https://doi.org/10.1016/j.jad.2008.06.009

Brewin, C. R., & Smart, L. (2005). Working memory capacity and suppression of intrusive thoughts. *Journal of Behavior Therapy and Experimental Psychiatry, 36*, 61–68. https://doi.org/10.1016/j.jbtep.2004.11.006

Britton, J. C., Lissek, S., Grillon, C., Norcross, M. A., & Pine, D. S. (2011). Development of anxiety: The role of threat appraisal and fear learning. *Depression and Anxiety, 28*, 5–17. https://doi.org/10.1002/da.20733

Caouette, J. D., & Guyer, A. E. (2014). Gaining insight into adolescent vulnerability for social anxiety from developmental cognitive neuroscience. *Developmental Cognitive Neuroscience, 8*, 65–76. https://doi.org/10.1016/j.dcn.2013.10.003

Carlson, S. M., & Moses, L. J. (2001). Individual differences in inhibitory control and children's theory of mind. *Child Development, 72*(4), 1032–1053. https://doi.org/10.1111/1467-8624.00333

Carlson, S. M., & Wang, T. A. (2007). Inhibitory control and emotion regulation in preschool children. *Cognitive Development, 22*, 489–510. https://doi.org/10.1016/j.cogdev.2007.08.002

Casey, B. J., Tottenham, N., Liston, C., & Durston, S. (2005). Imaging the developing brain: What have we learned about cognitive development? *TRENDS in Cognitive Sciences, 9*(3), 104–110. https://doi.org/10.1016/j.tics.2005.01.011

Cervenka, S., Hedman, E., Ikoma, Y., Djurfeldt, D. R., Rück, C., Halldin, C., & Lindefors, N. (2012). Changes in dopamine D2-receptor binding are associated to symptom reduction after psychotherapy in social anxiety disorder. *Translational Psychiatry, 2*(5), 1–7. https://doi.org/10.1038/tp.2012.40

Chronis-Tuscano, A., Degnan, K. A., Pine, D. S., Pérez-Edgar, K., Henderson, H. A., Diaz, Y., … Fox, N. A. (2009). Stable early maternal report of behavioral inhibition predicts lifetime social anxiety disorder in adolescence. *Journal of the American Academy of Child & Adolescent Psychiatry, 48*(9), 928–935. https://doi.org/10.1097/CHI.0b013e3181ae09df

Clauss, J. A., & Blackford, J. U. (2012). Behavioral inhibition and risk for developing social anxiety disorder: A meta-analytic study. *Journal of the American Academy of Child and Adolescent Psychiatry, 51*(10), 1066–1075. https://doi.org/10.1016/j.jaac.2012.08.002

Colzato, L. S., van den Wildenberg, W. P. M., van Wouwe, N. C., Pannebakker, M. M., & Hommel, B. (2009). Dopamine and inhibitory action control: Evidence from spontaneous eye blink rates. *Experimental Brain Research, 196*, 467–474. https://doi.org/10.1007/s00221-009-1862-x

Costa, V. D., Dal Monte, O., Lucas, D. R., Murray, E. A., & Averbeck, B. B. (2016). Amygdala and ventral striatum make distinct contributions to reinforcement learning. *Neuron, 92*, 505–517. https://doi.org/10.1016/j.neuron.2016.09.025

Cremers, H. R., Veer, I. M., Spinhoven, P., Rombouts, S. A. R. B., & Roelofs, K. (2015). Neural sensitivity to social reward and punishment anticipation in social anxiety disorder. *Frontiers in Behavioral Neuroscience, 8*(439), 1–9. https://doi.org/10.3389/fnbeh.2014.00439

Degnan, K. A., & Fox, N. A. (2007). Behavioral inhibition and anxiety disorders: Multiple levels of a resilience process. *Development and Psychopathology, 19*, 729–746. https://doi.org/10.1017/S0954579407000363

Diamond, A. (2006). The early development of executive functions. In E. Bialystok, & F. Craik (Eds.), *Lifespan Cognition: Mechanisms of Change* (pp. 70–95). New York: Oxford University Press.

Eggum-Wilkens, N. D., Reichenberg, R. E., Eisenberg, N., & Spinard, T. L. (2016). Components of effortful control and their relations to children's shyness. *International Journal of Behavioral Development, 40*(6), 544–554. https://doi.org/10.1177/0165025415597792

Eysenck, M. W., Derakshan, N., Santos, R., & Calvo, M. G. (2007). Anxiety and Cognitive Performance: Attentional Control Theory. *Emotion, 7*(2), 336–353. https://doi.org/10.1037/1528-3542.7.2.336

Fitzpatrick, C., McKinnon, R. D., Blair, C. B., & Willoughby, M. T. (2014). Do preschool executive function skills explain the school readiness gap between advantaged and disadvantaged children? *Learning and Instruction, 30*, 25–31. https://doi.org/10.1016/j.learninstruc.2013.11.003

Frank, M. J., Woroch, B. S., & Curan, T. (2005). Error-related negativity predicts reinforcement learning and conflict biases. *Neuron, 47*, 495–501. https://doi.org/10.1016/j.neuron.2005.06.020

Fu, X., Nelson, E. E., Borge, M., Buss, K. A., & Pérez-Edgar, K. (2019). Stationary and ambulatory attention patterns are differentially associated with early temperamental risk for socioemotional problems: Preliminary evidence from a multimodal eye-tracking investigation. *Development and Psychopathology, 31*, 971–988. https://doi.org/10.1017/S0954579419000427

Fu, X., & Pérez-Edgar, K. (2019). Threat-related attention bias in socioemotional development: A critical review and methodological considerations. *Developmental Review, 51*, 31–57. https://doi.org/10.1016/j.dr.2018.11.002

Fu, X., Taber-Thomas, B. C., & Pérez-Edgar, K. (2017). Frontolimbic functioning during threat-related attention: Relations to early behavioral inhibition and anxiety in children. *Biological Psychology, 122*, 98–109. https://doi.org/10.1016/j.biopsycho.2015.08.010

Gonzalez, M. Z., Allen, J. P., & Coan, J. A. (2016). Lower neighborhood quality in adolescence predicts higher mesolimbic sensitivity to reward anticipation in adulthood. *Developmental Cognitive Neuroscience, 22*, 48–57, 10.1016.j.dcn.2016.10.003.

Guyer, A. E., Choate, V. R., Detloff, A., Benson, B., Nelson, E. E., Pérez-Edgar, K., … Ernst, M. (2012). Striatal functional alteration during incentive anticipation in pediatric anxiety disorders. *American Journal of Psychiatry, 169*, 205–212. https://doi.org/10.1176/appi.ajp.2011.11010006

Guyer, A. E., Nelson, E. E., Pérez-Edgar, K., Hardin, M. G., Roberson-Nay, R., Monk, C. S., … Ernst, M. (2006). Striatal functional alteration in adolescents characterized by early childhood behavioral inhibition. *The Journal of Neuroscience, 26*(24), 6399–6405. https://doi.org/10.1523/JNEUROSCI.0666-06.2006
Hall, A. (1945). The origin and purposes of blinking. *British Journal of Ophthalmology, 29*(9), 445–467. https://doi.org/10.1136/bjo.29.9.445
Henderson, H. A., Pine, D. S., & Fox, N. A. (2015). Behavioral inhibition and developmental risk: A dual-processing perspective. *Neuropsychopharmacology, 40*, 207–224.
Henderson, H. A., & Wilson, M. J. G. (2017). Attention processes underlying risk and resilience in behaviorally inhibited children. *Current Behavioral Neuroscience Reports, 4*, 99–106. https://doi.org/10.1007/s40473-017-0111-z
Hirshfeld, D. R., Rosenbaum, J. F., Biederman, J., Bolduc, E. A., Faraone, S. V., Snidman, N., … Kagan, J. (1992). Stable behavioral inhibition and its association with anxiety disorder. *Journal of the American Academy of Child & Adolescent Psychiatry, 31*(1), 103–111. https://doi.org/10.1097/00004583-199201000-00016
Holroyd, C. B., & Coles, M. G. H. (2002). The neural basis of human error processing: Reinforcement learning, dopamine, and error-related negativity. *Psychological Review, 109*(4), 679–709. https://doi.org/10.1037/0033-295X.109.4.679
Hornykiewicz, O. (1966). Dopamine (3-Hydroxytyramine) and brain function. *Pharmacological Review, 18*(2), 925–964.
Humphreys, K. L., Lee, S. S., Gabard-Durnam, L. J., Goff, B., Flannery, J., & Tottenham, N. (2015). Exploration-exploitation strategy is dependent on early experience. *Developmental Psychobiology, 313–321*. https://doi.org/10.1002/dev/21293
Jarcho, J. M., & Guyer, A. E. (2018). The neural mechanisms of behavioral inhibition. In K. Pérez-Edgar, & N. A. Fox (Eds.), *Behavioral inhibition: Integrating theory, research, and clinical perspectives* (pp. 237–261). Cham, Switzerland: Springer.
Johnson, M. J. (2001). Functional brain development in humans. *Nature Reviews Neuroscience, 2*, 475–483. https://doi.org/10.1038/35081509
Jongkees, B. J., & Colzato, L. S. (2016). Spontaneous eye blink rate as a predictor of dopamine-related cognitive function - A review. *Neuroscience and Biobehavioral Reviews, 71*, 58–82. https://doi.org/10.1016/j.neubiorev.2016.08.020
Kagan, J., Reznick, J. S., & Snidman, N. (1988). Biological bases of childhood shyness. *Science, 240*(4849), 167–171. https://doi.org/10.1126/science.3353713
Karlsson, S., Rieckmann, A., Karlsson, P., Farde, L., Nyberg, L., & Bäckman, L. (2011). Relationship of dopamine D1 receptor binding in striatal and extrastriatal regions to cognitive functioning in healthy humans. *Neuroimage, 57*, 346–351. https://doi.org/10.1016/j.neuroimage.2011.04.047
Karson, C. N. (1983). Spontaneous eye-blink rates and dopaminergic systems. *Brain, 106*(3), 643–653. https://doi.org/10.1093/brain/106.3.643
Kooijmans, R., Scheres, A., & Oosterlaan, J. (2000). Response inhibition and measures of psychopathology: A dimensional analysis. *Child Neuropsychology, 6*(3), 145–184. https://doi.org/10.1076/chin.6.3.175.3154
Ladouce, S., Donaldson, D. I., Dudchenko, P. A., & Ietswaart, M. (2017). Understanding minds in real-world environments: Toward a mobile cognition approach. *Frontiers in Human Neuroscience, 10*(684), 1–14. https://doi.org/10.3389/fnhum.2016.00694
Lahat, A., Lamm, C., Chronis-Tuscano, A., Pine, D. S., Henderson, H. A., & Fox, N. A. (2014). Early behavioral inhibition and increased error monitoring predict later social phobia symptoms in childhood. *Journal of the American Academy of Child and Adolescent Psychiatry, 53*(4), 447–455. https://doi.org/10.1016/j.jaac.2013.12.019
Lamm, C., Walker, O. L., Degnan, K. A., Henderson, H. A., Pine, D. S., McDermott, J. M., & Fox, N. A. (2014). Cognitive control moderates early childhood temperament in predicting social behavior in seven year old children: An ERP study. *Developmental Science, 17*(5), 667–681. https://doi.org/10.1111/desc.12158
Lengua, L. J. (2003). Associations among emotionality, self-regulation, adjustment problems, and positive adjustment in middle childhood. *Applied Developmental Psychology, 24*, 595–618. https://doi.org/10.1016/j.appdev.2003.08.002
Lonigan, C. J., Vasey, M. W., Phillips, B. M., & Hazen, R. A. (2004). Temperament, anxiety, and the processing of threat-relevant stimuli. *Journal of Clinical Child and Adolescent Psychology, 33*(1), 8–20. https://doi.org/10.1207/S15374424JCCP3301_2
Lumme, V., Aalto, S., Ilonon, T., Någren, K., & Hietala, J. (2007). Dopamine D2/D3 receptor binding in the anterior cingulate cortex and executive functioning. *Psychiatry Research: Neuroimaging, 156*(1), 69–74. https://doi.org/10.1016/j.pscychresns.2006.12.012
McDermott, J. M., Pérez-Edgar, K., Henderson, H. A., Chronis-Tuscano, A., Pine, D. S., & Fox, N. A. (2009). A history of child behavioral inhibition and enhanced response monitoring in adolescence are linked to clinical anxiety. *Biological Psychiatry, 65*, 445–448. https://doi.org/10.1016/j.biopsych.2008.10.043
McNab, F., Varrone, A., Farde, L., Jucaite, A., Bystrinsky, P., Forssberg, H., & Klingberg, T. (2009). Changes in cortical dopamine D1 receptor binding associated with cognitive training. *Science, 323*(5915), 800–802. https://doi.org/10.1126/science.1166102
Miyake, A., Friedman, N. P., Emerson, M. J., Witzki, A. H., Howerter, A., & Wager, T. D. (2000). The unity and diversity of executive functions and their contributions to complex "frontal lobe" tasks: A latent variable analysis. *Cognitive Psychology, 41*(1), 49–100. https://doi.org/10.1006/cogp.1999.0734
Mkrtchian, A., Aylward, J., Dayan, P., Rosier, J. P., & Robinson, O. J. (2017). Modeling avoidance in mood and anxiety disorders using reinforcement learning. *Biological Psychiatry, 82*, 532–539. https://doi.org/10.1016/j.biopsych.2017.01.017
Moraga-Amaro, R., Gonzalez, H., Pacheco, R., & Stehberg, J. (2014). Dopamine receptor D3 deficiency results in chronic depression and anxiety. *Behavioural Brain Research, 274*, 186–193. https://doi.org/10.1016/j.bbr.2014.07.055
Morales, S., Taber-Thomas, B. C., & Pérez-Edgar, K. (2017). Patterns of attention to threat across tasks in behaviorally inhibited children at risk for anxiety. *Developmental Science, 20*. https://doi.org/10.1111/desc.12391
Moran, T. P. (2016). Anxiety and working memory capacity: A meta-analysis and narrative review. *Psychological Bulletin, 142*(8), 1–34. https://doi.org/10.1037/bul0000051
Northoff, G., & Tumati, S. (2019). "Average is good, extremes are bad" - Non-linear inverted U-shaped relationship between neural mechanisms and functionality of mental features. *Neuroscience and Biobehavioral Reviews, 104*, 11–25. https://doi.org/10.1016/j.neubiorev.2019.06.030
Pérez de la Mora, M., Gallegos-Cari, A., Arizmendi-Garcia, Y., Marcellino, D., & Fuxe, K. (2010). Role of dopamine receptor mechanisms in the amygdaloid modulation of fear and anxiety: Structural and functional analysis. *Progress in Neurobiology, 90*, 198–216. https://doi.org/10.1016/j.pneurobio.2009.10.010
Pérez-Edgar, K., Bar-Haim, Y., McDermott, J. M., Chronis-Tuscano, A., Pine, D. S., & Fox, N. A. (2010). Attention biases to threat and behavioral inhibition in early childhood shape adolescent social withdrawal. *Emotion, 10*(3), 349–1257. https://doi.org/10.1037/a0018486
Pérez-Edgar, K., Hardee, J. E., Guyer, A. E., Benson, B. E., Nelson, E. E., Gorodetsky, E., … Ernst, M. (2014). DRD4 and striatal modulation of the link between childhood behavioral inhibition and adolescent anxiety. *Social, Cognitive, and Affective Neuroscience, 9*, 445–453. https://doi.org/10.1093/scan/nst001
Pérez-Edgar, K. (2018). Attention mechanisms in behavioral inhibition: Exploring, and exploiting, the environment. In K. Pérez-Edgar, & N. A. Fox (Eds.), *Behavioral inhibition: Integrating theory, research, and clinical perspectives* (pp. 237–261). Cham, Switzerland: Springer.
Richey, J. A., Rittenberg, A., Hughes, L., Damiano, C. R., Sabatino, A., Miller, S., … Dichter, G. S. (2014). Common and distinct neural features of social and non-social reward processing in autism and social anxiety disorder. *Social, Cognitive, and Affective Neuroscience, 9*, 367–377. https://doi.org/10.1093/scan/nss146
Risko, E. F., Richardson, D. C., & Kingstone, A. (2016). Breaking the fourth wall of cognitive science: Real-world social attention and the dual function of gaze. *Current Directions in Psychological Science, 25*(1), 70–74. https://doi.org/10.1177/0963721415617806
Roy, A. K., Vasa, R. A., Bruck, M., Mogg, K., Bradley, B. P., Sweeney, M., … Pine, D. S. (2008). Attention bias toward threat in pediatric anxiety disorders. *Journal of the American Academy of Child and Adolescent Psychiatry, 47*(10), 1189–1196. https://doi.org/10.1097/CHI.0b013e3181825ace
Rubin, K. H., Burgess, K. B., & Hastings, P. D. (2002). Stability and social-behavioral consequences of toddlers' inhibited temperament and parenting behaviors. *Child Development, 73*(2), 483–495. https://doi.org/10.1111/1467-8624.00419
Samochowiec, J., Hajduk, A., Samochowiec, A., Horodnicki, J., Stępień, G., Grzywacz, A., & Kucharska-Mazur, J. (2004). Association studies of MAO-A, COMT, and 5-HTT genes polymorphisms in patients with anxiety disorders of the phobic spectrum. *Psychiatry Research, 128*(1), 21–26. https://doi.org/10.1016/j.psychres.2004.05.012
Santesso, D. L., Evins, A. E., Frank, M. J., Schetterm, E. C., Bogdanm, R., & Pizzagalli, D. A. (2009). Single dose of a dopamine agonist impairs reinforcement learning in humans: Evidence from event-related potentials and computational modeling of striatal-cortical function. *Human Brain Mapping, 30*, 1963–1976. https://doi.org/10.1002/hbm.20642
Schillerstrom, J. E., Horton, M. S., & Royall, D. R. (2005). The impact of medical illness on executive function. *Psychosomatics, 46*(6), 508–516. https://doi.org/10.1176/appi.psy.46.6.508

Schmidt, L. A., Fox, N. A., Pérez-Edgar, K., & Hamer, D. H. (2009). Linking gene, brain, and behavior: DRD4, frontal asymmetry, and temperament. *Psychological Science, 20*(7), 831–837. https://doi.org/10.1111/j.1467-9280.2009.02374.x

Schmidt, L. A., Fox, N. A., Pérez-Edgar, K., Hu, S., & Hamer, D. H. (2001). Association of DRD4 with attention problems in normal childhood development. *Psychiatric Genetics, 11*, 25–29. https://doi.org/10.1097/00041444-200103000-00005

Shin, N. Y., Lee, T. Y., Kim, E., & Kwon, J. S. (2014). Cognitive functioning in obsessive-compulsive disorder: A meta-analysis. *Psychological Medicine, 44*(6), 1121–1130. https://doi.org/10.1017/S0033291713001803

Silk, J. S., Davis, S., McMakin, D. L., Dahl, R. E., & Forbes, E. E. (2012). Why do anxious children become depressed teenagers? The role of social evaluative threat and reward processing. *Psychological Medicine, 42*(10), 2095–2107. https://doi.org/10.1017/S0033291712000207

Slagter, H. A., Georgopoulou, K., & Frank, M. J. (2015). Spontaneous eye blink rate predicts learning from negative, but not positive, outcomes. *Neuropsychologia, 71*, 126–132. https://doi.org/10.1016/j.neuropsychologia.2015.03.028

Snyder, H. R., Miyake, A., & Hankin, B. L. (2015). Advancing understanding of executive function impairments and psychopathology: Bridging the gap between clinical and cognitive approaches. *Frontiers in Psychology, 6*(328), 1–24. https://doi.org/10.3389/fpsyg.2015.00328

Stein, M. B., Fallin, M. D., Schork, N. J., & Gelernter, J. (2005). COMT polymorphisms and anxiety-related personality traits. *Neuropsychopharmacology, 30*, 2092–2102.

Suveg, C., & Zeman, J. (2004). Emotion regulation in children with anxiety disorders. *Journal of Clinical Child and Adolescent Psychology, 33*(4), 750–759. https://doi.org/10.1207/s15374424jccp3304_10

Takahashi, H., Kato, M., Takano, H., Arakawa, R., Okumura, M., Otsuka, T., … Suhara, T. (2008). Differential contributions of prefrontal and hippocampal dopamine D1 and D2 receptors in human cognitive functions. *The Journal of Neuroscience, 28*(46), 12032–12038. https://doi.org/10.1523/JNEUROSCI.3446-08.2008

Thompson-Schill, S. L., Ramscar, M., & Chrysikou, E. G. (2009). Cognition without control: When a little frontal lobe goes a long way. *Current Directions in Psychological Science, 18*(5), 259–263. https://doi.org/10.1111/j.1467-8721.2009.01648.x

Thorell, L. B., Bohlin, G., & Rydell, A. (2004). Two types of inhibitory control: Predictive relations to social functioning. *International Journal of Behavioral Development, 28*(3), 193–203. https://doi.org/10.1080/01650250344000389

Toren, P., Sadeh, M., Wolmer, L., Eldar, S., Koren, S., Weizman, R., & Laor, N. (2000). Neurocognitive correlates of anxiety disorders in children: A preliminary report. *Journal of Anxiety Disorders, 14*(3), 239–247. https://doi.org/10.1016/s0887-6185(99)00036-5

Van Slooten, J. C., Jahfari, S., & Theeuwes, J. (2019). Spontaneous eye blink rate predicts individual differences in exploration and exploitation during reinforcement learning. *Nature Scientific Reports, 9*(17436). https://doi.org/10.1038/s41598-019-53805-y

Welsh, M. C., Pennington, B. F., & Groisser, D. B. (1991). A normative-developmental study of executive function: A window on prefrontal function in children. *Developmental Neuropsychology, 7*(2), 131–149. https://doi.org/10.1080/87565649109540483

White, L. K., McDermott, J. M., Degnan, K. A., Henderson, H. A., & Fox, N. A. (2011). Behavioral Inhibition and anxiety: The moderating roles of inhibitory control and attention shifting. *Journal of Abnormal Child Psychology, 39*, 735–747. https://doi.org/10.1007/s10802-011-9490-x

Wolfe, C. D., & Bell, M. A. (2014). Brain electrical activity of shy and non-shy preschool-aged children during executive function tasks. *Infant and Child Development, 23*(3), 259–272. https://doi.org/10.1002/icd.1858

Zarrindast, M., & Khakpai, F. (2015). The modulatory role of dopamine in anxiety-like behavior. *Archives of Iranian Medicine, 18*(9), 591–603.

Zelazo, P. D. (2020). Executive Function and Psychopathology: A Neurodevelopmental Perspective. *Annual Review of Clinical Psychology, 16*, 431–454. https://doi.org/10.1146/annurev-clinpsy-072319-024242

Zelazo, P. D., Carlson, S. M., & Kesek, A. (2008). The development of executive function in childhood. In C. A. Nelson, & M. Luciana (Eds.), *Developmental cognitive neuroscience. Handbook of developmental cognitive neuroscience* (pp. 553–574). MIT Press.

Zhang, T., Mou, D., Wang, C., Tan, F., Jiang, Y., Lijun, Z., & Li, H. (2015). Dopamine and executive function: Increased spontaneous eye blink rates correlate with better set-shifting and inhibition, but poorer updating. *International Journal of Psychophysiology, 96*, 155–161. https://doi.org/10.1016/j.ijpsycho.2015.04.010