Contributions of dopamine-related basal ganglia neurophysiology to the developmental effects of incentives on inhibitory control

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ABSTRACT

Inhibitory control can be less reliable in adolescence, however, in the presence of rewards, adolescents' performance often improves to adult levels. Dopamine is known to play a role in signaling rewards and supporting cognition, but its role in the enhancing effects of reward on adolescent cognition and inhibitory control remains unknown. Here, we assessed the contribution of basal ganglia dopamine-related neurophysiology using longitudinal MR-based assessments of tissue iron in rewarded inhibitory control, using an antisaccade task. In line with prior work, we show that neutral performance improves with age, and incentives enhance performance in adolescents to that of adults. We find that basal ganglia tissue iron is associated with individual differences in the magnitude of this reward boost, which is strongest in those with high levels of tissue iron, predominantly in adolescence. Our results provide novel evidence that basal ganglia neurophysiology supports developmental effects of rewards on cognition, which can inform neurodevelopmental models of the role of dopamine in reward processing during adolescence.

1. Introduction

Adolescence is a period of heightened sensation seeking and reward-driven behaviors (Dahl, 2004; L.P. Spear, 2000a, 2000b; Stansfield and Kirstein, 2006), which are thought to be adaptive for gaining novel experiences and specializing the neurobiological pathways required to transition to independence in adulthood (Luna et al., 2015; Murty et al., 2016; Steinberg, 2004). However, sensation seeking can lead to risk-taking behaviors that have long term consequences (e.g., reckless driving, risky sexual behavior, substance use; see (Shulman et al., 2016 for review). Neurodevelopmental models, including the Driven Dual Systems model (Luna and Wright, 2016; Shulman et al., 2016), propose that developmental changes in dopamine (DA) and reward system function underlie this peak in sensation seeking (Shulman et al., 2016), supported by a relative predominance of reward systems over cognitive control systems (including inhibitory control) that bias adolescent decision-making toward rewarding stimuli (Luna and Wright, 2016; Shulman et al., 2016). Though we are beginning to understand how DA

function supports reward-driven behaviors during adolescence in both animal models (Andersen et al., 1997; Luciana et al., 2012; Wahlstrom et al., 2010) and human studies (Reynolds and Flores, 2021), far less is known about the role of DA in interactions between developmentally-relevant reward and inhibitory control systems.

In parallel with developmental changes in DAergic function, inhibitory control, which involves the suppression of task-irrelevant responses in lieu of goal-directed responses, continues to undergo maturational changes through adolescence (Alahyane et al., 2014; Fischer et al., 1997; Klein and Foerster, 2001; Levin et al., 1991; Liston et al., 2006; Luna et al., 2004, 2004; Munoz et al., 1998; Ordaz et al., 2013; Ridderinkhof and van der Molen, 1997; Velanova et al., 2008; Williams et al., 1999). The antisaccade (AS) task is a well-validated assessment of inhibitory control (Constantinidis and Luna, 2019; Munoz and Everling, 2004) that consitently demonstrates age-related decreases in inhibitory errors and latency through adolescence into adulthood (Constantinidis and Luna, 2019). Within this task, participants are instructed to direct their gaze away from a salient

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periphereally presented stimulus, engaging executive processes that suppress a prepotent saccade in favor of a goal-directed saccade to it's mirror location (Hallett, 1978; Munoz and Everling, 2004). The AS task recruits both cognitive- and reward-relevant circuitry, including a distribtued fronto-parietal network comprised of the frontal, supplementary, and parietal eye fields, the dorsolateral prefrontal cortex, and the anterior cingulate cortex (Brown et al., 2007; Connolly et al., 2005, 2002; Curtis and Connolly, 2008; Curtis and D'Esposito, 2003; DeSouza et al., 2003; Ford et al., 2005; Velanova et al., 2008), in addition to regions of the basal ganglia (Coe et al., 2019; Hikosaka et al., 2000; Munoz et al., 2000; Munoz and Everling, 2004), respectively. Developmental improvements in AS performance are supported by concomittant changes across these networks through adolescence into adulthood (Alahyane et al., 2014; Geier et al., 2010; Hallquist et al., 2018; Ordaz et al., 2013).

Interactions between reward and cognitive systems (reward-cognition interactions) are important for optimal decision-making (Soltani and Wang, 2008; Vassena et al., 2014), and change through adolescence to support refinements into adulthood (Geier, 2013; Larsen et al., 2017; Luna et al., 2013; Van Duijvenvoorde et al., 2016). Importantly, several studies have shown that in the presence of incentives (rewards), adolescent inhibitory control reaches adult-like levels, with fewer errors and faster latencies (Duka and Lupp, 1997; Geier et al., 2010; Geier and Luna, 2012; Hallquist et al., 2018; Hardin et al., 2007; Hawes et al., 2017; Jazbec et al., 2005, 2006; Luna et al., 2013; Padmanabhan et al., 2011; Paulsen et al., 2015; Zhai et al., 2015), providing support for a Driven Dual Systems model of adolescent behavior whereby cognitive control circuits are driven in service of obtaining rewards (Luna and Wright, 2016; Shulman et al., 2016). This 'reward boost' is accompanied by heightened activation within reward processing regions, including the nucleus accumbens (Geier et al., 2010; Hallquist et al., 2018; Padmanabhan et al., 2011) and the ventromedial prefrontal cortex (Hallquist et al., 2018; Zhai et al., 2015), in addition to enhanced activation wtihin critical regions of the oculomotor network, including the frontal eye fields (Geier et al., 2010). This ability for rewards to potentiate inhibitory control diminishes by late adolescence as AS performance peaks and stabilizes (Geier et al., 2010; Hallquist et al., 2018). Although enhanced reward-related activation may drive improvements in inhibitory control across development, the role of DA-related processes, known to support reward-cognition interactions, in this adolescent 'reward boost' remain unknown.

Our understanding of the role of DA in the development of inhibitory control and reward-cognition interactions during human adolescence has been limited due to challenges in the use of positron emission tomography (PET) in pediatric populations that would provide in vivo indices of DA function. To overcome these limitations, we leveraged brain tissue iron, a property of basal ganglia neurobiology that is known to be linked to the structure and function of the DA system and can be readily assessed using MRI. Tissue iron is involved in several aspects of neuronal functioning, including cellular respiration (Ward et al., 2014), myelination (Connor and Menzies, 1996; Todorich et al., 2009), and monoamine synthesis (Lu et al., 2017; Youdim, 2018; Youdim and Green, 1978). In particular, tissue iron is involved in DA synthesis and production, and co-localizes with DA vesicles (Ortega et al., 2007), is a co-factor for tyrosine hydroxylase (Ortega et al., 2007; Zucca et al., 2017), the rate limiting step in DA synthesis, and is located in the dendrites of DA neurons (Torres-Vega et al., 2012). Importantly, tissue iron is found in highest concentrations within DAergic regions, including the basal ganglia and midbrain (Brass et al., 2006; Connor et al., 1990; Hallgren and Sourander, 1958; Morris et al., 1992; Thomas et al., 1993), and MR-based indices of tissue iron within the nucleus accumbens have been shown to correspond to presynaptic vesicular DA storage measured using PET [^{11}C]dihydrotetrabenazine (DTBZ; Kilbourn, 2014; Larsen et al., 2020b). These findings therefore suggest that important aspects of DA-related basal ganglia neurophysiology are reflected in tissue iron properties. Indices of tissue iron have therefore

been used to probe the integrity of the basal ganglia in disorders involving DAergic dysfunction, such as ADHD (Adisetiyo et al., 2014; Cortese et al., 2012; Sethi et al., 2017), cocaine addiction (Ersche et al., 2017), Parkinson's disease (Piao et al., 2017; Zucca et al., 2017), Huntington's disease (Ward et al., 2014), and restless leg syndrome (Allen and Earley, 2007; Connor et al., 2011; Khan et al., 2017). More recently, studies have characterized developmental increases in tissue iron accrual across the basal ganglia throughout the first two decades of life, the rate of which decreases into adulthood (Aquino et al., 2009; Hallgren and Sourander, 1958; Hect et al., 2018; Larsen et al., 2020a, 2020b; Larsen and Luna, 2015; Peterson et al., 2019), and have further demonstrated an association between striatal tissue iron concentration and developmental trajectories in functional connectivity across reward networks (Parr et al., 2021) and cognitive function through adolescence (Hect et al., 2018; Larsen et al., 2020a). Here, we tested whether normative variation in basal ganglia tissue iron, given its role in DAergic processes, supports the enhancing effects of rewards on cognitive control in adolescence.

In order to determine the role of basal ganglia DA-related neurobiology in developmental changes in the modulation of cognitive control by exogenous rewards, we designed a longitudinal developmental neuroimaging study that characterized age-related changes in AS performance with in both rewarded and neutral contexts (n = 193 sessions, 12–33 years of age, 1–3 visits). We assessed the role of basal ganglia neurophysiology using longitudinal MRI-based assessments of tissue iron obtained via normalizing and time-averaging T2* -weighted images of task and resting state scans (nT2*w; n = 177 sessions, 12–33 years of age, 1–3 visits), which quantifies the relative T2* relaxation across the brain and is sensitive to magnetic field inhomogeneities induced by iron (Brown et al., 2014; Langkammer et al., 2010; Larsen and Luna, 2015; Peterson et al., 2019; Price et al., 2021; Schenck and Zimmerman, 2004). Given recent findings showing a specific role for NAcc tissue iron in the development of frontostriatal networks (Parr et al., 2021) and putamen tissue iron in the development of general cognitive performance (Larsen et al., 2020a), we explored the contribution of nT2*w extracted separately across basal ganglia subregions. We examined the extent to which variability in in vivo indices of tissue iron contributed to the level of reward-related modulation of AS performance, and critically, whether the relationship between tissue iron and the 'reward boost' to AS performance changed with age. We hypothesized that tissue iron would have greater involvement in reward trials relative to neutral, given its correspondence with DAergic processes and their role in reward processing, and within the framework of the Driven Dual Systems model (Luna and Wright, 2016; Shulman et al., 2016), we hypothesized that this relationship would be most prominent in adolescence when reward systems and DAergic processing is heightened (reflected in the 'reward boost' that is most evident during this period), waning into adulthood.

2. Materials and methods

2.1. Participants

One hundred and fifty-five adolescents and young adults participated in an accelerated longitudinal study that included behavioral and MRI sessions (82 females, age range, 12 −31). One hundred and thirteen participants also returned for a second visit (58 females, age range, 13.5–33), and seventy-six returned for a third visit (35 females, age range, 15–34). Visits were approximately 18 months apart, and a total of 346 sessions were initially included. Participants were recruited from the community and were screened for the absence of psychiatric and neurological problems including loss of consciousness, self or first-degree relatives with major psychiatric illness, and contraindications to MRI (e.g., claustrophobia, metal in the body, pregnancy). Participants or the parents of minors gave informed consent with those less than 18 years of age providing assent. All experimental procedures were

approved by the University of Pittsburgh Institutional Review Board and complied with the Code of Ethics of the World Medical Association (Declaration of Helsinki, 1964). Participants 18 years of age and older underwent simultaneous PET acquisition, and previous publications have been reported on this line of inquiry (Calabro et al., 2020; Larsen et al., 2020b; Parr et al., 2021). Here, given that the current research question was developmental in nature, we included MR-based indices of tissue iron that were collected across the entire adolescent and young adult sample. We include an expanded age-range that allowed us to capture stabilization of processes into adulthood, as there is increasing evidence for continued neurodevelopmental changes, including synaptic pruning (Petanjek et al., 2011), white matter development (Simmonds et al., 2017), and cognitive performance (Ordaz et al., 2013).

2.2. Eye tracking data acquisition

Eye tracking data were acquired using a Long-Range Optics System (Applied Science Laboratories; Model 6000; Bedford, MA) in the MR scanner. Eye-position was recorded via pupil-corneal reflection obtained by a head coil-mounted mirror with 0.5° of visual angle (details have been previously reported in Geier et al., 2010; Hallquist et al., 2018; Paulsen et al., 2015). A 9-point calibration routine was performed at the beginning of the experimental scan and between runs when necessary. Stimuli were presented using E-prime software (Psychology Software Tools, Inc., Pittsburgh, PA) and back projected onto a screen behind the magnet bore, viewed by the participant on a head coil-mounted mirror. Data were scored offline using ILAB (Gitelman, 2002) and MATLAB software (Mathworks, Inc.). Manual inspection was also performed to ensure accuracy of the automated scoring algorithm. Participants completed a behavioral laboratory session approximately one week prior to the fMRI scan to ensure that task instructions were understood and they were able to perform to antisaccade task. During this session, participants completed 54 trials total of the task described below across 6 runs performed outside of the scanner.

2.3. Antisaccade task

Participants completed 25 trials each of a rewarded- and neutral-antisaccade (AS) task (50 trials total; Fig. 1, described in (Geier et al., 2010; Padmanabhan et al., 2011; Quach et al., 2020; Tervo-Clemmens et al., 2017) across six neuroimaging runs performed in the scanner during fMRI acquisition. Each trial included four epochs (Fig. 1; cue, preparation, response, and feedback). Full trials began with a cue epoch (1.5 s) which signaled either the availability of reward (diamonds in Fig. 1) or neutral (grey ellipse in Fig. 1). Next, a fixation cross appeared, indicating the preparation epoch (1.5 s), followed by the response period (1.5 s) in which a peripheral cue was presented along the horizontal meridian at 1 of 2 eccentricities ($\pm 6°$ and $9°$ visual angle relative to fixation). Participants were instructed to direct their gaze away from the visual stimulus to the mirror location. Finally, feedback was presented (1.5 s) which consisted of a "cha-ching" (like a cash register) and "buzzer" sound for correct and incorrect AS performance, respectively. Trials with latencies of < 100 ms (express saccade latency) were excluded from analysis as they were deemed anticipatory and not involving cognitive processes. Reward and neutral trials were displayed in an interleaved fashion (pseudorandomly), and were presented as "bonus trials" that were embedded within a reward-learning task (not presented here, but described previously in Calabro et al., 2020; Parr et al., 2021). Participants were instructed that correct performance of these "bonus trials" provided a chance for them to win extra points, resulting in extra payment up to $25 at the end of the session. In practice, all participants received the additional $25, regardless of their AS task performance. Points were used as opposed to actual monetary values during the task in order to control for age-related differences in the impact of $25 and to minimize participants ability to track the total of dollar amounts during the task (as has been the approach described

Anti-Saccade Task Design
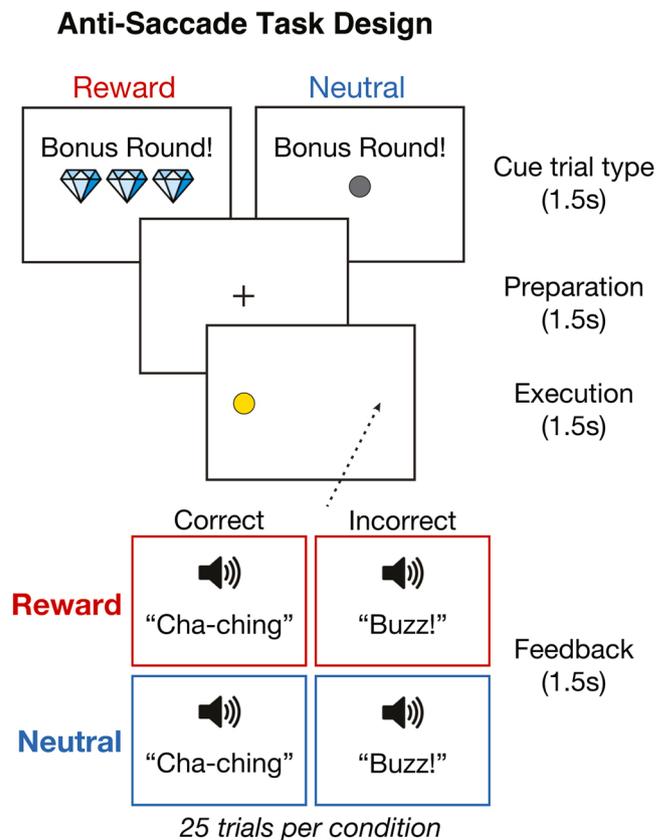
Fig. 1. Antisaccade task design. Participants completed 25 trials each of a rewarded- and neutral- antisaccade task. Each trial began with a cue epoch that signaled the availability of reward (in red) or indicated a neutral trial (in blue). Participants were instructed to direct their gaze away from the visual stimulus to its mirror location. Auditory feedback was provided for correct (cha ching) and incorrect (buzz) responses.

previously in Geier et al., 2010; Geier and Luna, 2012; Hallquist et al., 2018; Hawes et al., 2017; Padmanabhan et al., 2011; Paulsen et al., 2015; Zhai et al., 2015).

Correct trials were defined as those in which the first eye movement during the response epoch with a velocity of $\geq 30°/s$ (Gitelman, 2002) was made toward the mirror location of the peripheral cue and exceeded the $2.5°/$visual angle central fixation window. Error trials were defined as those in which the first saccade in the response epoch was directed toward the peripheral stimulus and extended beyond the $2.5°/$visual angle central fixation window. Trials in which no saccade was generated (non-response trials) were excluded from further analyses.

Participants with fewer than 20 correct trials total (out of 50, $< 40\%$ accuracy, or substantial data loss from poor eye tracking) were excluded from further analysis, which resulted in the exclusion of 153 sessions. Following exclusions, AS data were obtained in 78 12–31 year old participants (38 females) at visit 1, 73 14–32 year olds at visit 2 (34 females), and 42 15–33 year olds at visit 3 (20 females), for a total of 193 sessions. Exclusion on the basis of performance was not significantly associated with participant age (mean age in excluded participants: 20.56, mean age in included participants: 21.36; $t = -1.16$, $p = .25$). Sessions with useable eye tracking data are depicted in Fig. S1.

2.4. MR data acquisition & preprocessing of T2*-weighted data

MRI data was acquired over 90 min on a 3 T Siemens Biograph mMR PET/MRI scanner. Participants' heads were immobilized using pillows placed inside the head coil, and participants were fitted with earbuds for auditory feedback and to minimize scanner noise. Structural images

were acquired using a T1 weighted magnetization-prepared rapid gradient-echo (MPRAGE) sequence (TR, 2300 ms; echo time (TE), 2.98 ms; flip angle, 9°; inversion time (T1), 900 ms; voxel size, 1.0 × 1.0 × 1.0 mm). Functional images were acquired using blood oxygen level dependent (BOLD) signal from an echoplanar sequence (TR, 1500 ms; TE, 30 ms; flip angle, 50°; voxel size, 2.3 ×2.3 mm in-plane resolution) with contiguous 2.3 mm – thick slices aligned to maximally cover the cortex and basal ganglia. Thirty minutes (six 5-min blocks) of task-based fMRI data were collected, as well as to 16 min (two 8 min scans) of fixation resting-state data prior to (pre-task) and following (post-task) the task.

Structural MRI data were preprocessed to extract the brain from the skull and warped to the MNI standard brain using both linear (FLIRT) and non-linear (FNIRT) transformations. T2* data, including fMRI and resting-state data, were preprocessed in a minimal fashion, including 4D slice-timing and head motion correction, skull stripping, coregistration to the structural image, and nonlinear warping to MNI space.

2.5. Time-averaging and normalization of nT2*w data

Distinct from typical fMRI BOLD studies that are interested in fluctuations in the T2* -weighted signal that change across time, here we were interested in the time-invariant aspects of the T2* -weighted signal that have been shown to reflect tissue-iron properties (Larsen and Luna, 2015). Preprocessing procedures for T2* -weighted images have been described in (Larsen and Luna, 2015; Peterson et al., 2019; Price et al., 2021; Vo et al., 2011) and include the following steps. First, each volume was normalized to the whole-brain mean (z-score normalization Larsen and Luna, 2015; Peterson et al., 2019), using a coverage map created from all inputs for each participant that included only non-zero values. Next, the normalized signal was aggregated voxel-wise across all volumes, including both task runs and resting state, using the median, which reduced the impact of outlier volumes, resulting in one normalized T2* -weighted image for each participant (nT2*w). High motion time points were identified as volumes containing frame-wise displacement (FD) > 0.3 mm, and were excluded from analyses (Siegel et al., 2014). Averaging across time enhances the signal to noise ratio (Larsen and Luna, 2015), while the normalization step gives the T2* decay in the basal ganglia relative to the whole brain, and allows for comparison of nT2*w values across participants. Here, we averaged across all functional and resting state runs, in line with prior research showing excellent reliability of this measure within sessions (ICCs ranging from.93 to.91 for within-session estimates of nT2*w values within basal ganglia ROIs; Price et al., 2021).

nT2*w values were extracted separately across each basal ganglia region of interest (ROI), including the pallidum, nucleus accumbens (NAcc), putamen, and caudate nucleus, using the Harvard-Oxford subcortical atlas (Jenkinson et al., 2011). Regional nT2*w values reflect the mean across all voxels in each region across both hemispheres (left and right combined). nT2*w values were included in the behavioral analysis detailed below as an index of basal ganglia dopamine neurobiology. In all behavioral analyses, we first tested for significant interactions with ROI to assess the specificity of the tissue iron effects across regions. In the case of significant interactions, we further interrogated relationships separately across each ROI. As we found no significant interaction terms, ROI was modelled as a covariate.

nT2*w indices of basal ganglia physiology were available in 78 12 – 31 year old participants (37 female) at visit 1, 73 14 – 32 year olds at visit 2 (33 female), and 38 17 – 32 year olds at visit 3 (18 female) for a total of 189 sessions in the participants for which good eye tracking data were available. One extreme outlier in the nT2*w values was detected and was not included in the final analyses (n = 1 from visit 2). Following this exclusion, a total of 188 sessions were included in the nT2*w analyses. Sessions with useable tissue iron data are depicted in Fig. S1.

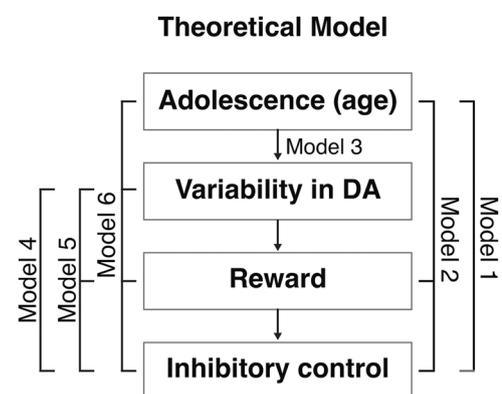### 2.6. Statistical analysis of behavioral data

The theoretical model that we are testing proposes that reward-related DAergic function will have a unique effect of enhancing inhibitory control in adolescence. Thus, we applied sequential models, described below, to test for main effect of age on correct response rate (Model 1), age by trial type interaction on correct response rate (Model 2), main effects of age on tissue iron (Model 3), main effects of tissue iron on correct response rate (Model 4), tissue iron by trial type interactions on correct response rate (Model 5), and finally, the full model tests for tissue iron by trial type by age interactions on correct response rate (Model 6). See Fig. 2 for the theoretical model describing our analysis strategy.

2.6.1. Behavioral variables

Correct response rate was calculated as the proportion of trials over all responses (excluding dropped trials) in which participants made a correct saccade to the mirror location of the target. Correct response latency was calculated as the time from stimulus appearance to the onset of the saccadic eye movement. Finally, as a measure of variability in latencies, we calculated standard deviation (latency (SD)). Parallel results for latency and SD are found in the supplemental section.

2.6.2. Reward enhancement to antisaccade performance

We first tested for significant effects of reward (trial type, reward or neutral) on antisaccade performance using generalized additive mixed models (GAMMs; *mgcv* package in R (Simpson, 2017), version 3.5.2 via RStudio version 1.1.1; https://www.r-project.org/), including random intercepts estimated for each participant in order to account for the longitudinal nature of the dataset. A smoothed term for age (s(age)) and sex were included as covariates in the models, and we tested for reward type by sex interactions and this term was removed from the models as it was not significant and modeled as a covariate (see Model 1 for final model). Age was modelled as a smoothed term to allow for non-linear effects of age, which may provide a better fit for modeling developmental changes through adolescence (Luna et al., 2004; Murty et al., 2018; Ordaz et al., 2013; Simmonds et al., 2017).

Fig. 2. Analyses of our theoretical model. The boxes represent our theoretical model proposing that reward-related DAergic function will have a unique effect of enhancing inhibitory control through adolescence. The brackets depict the associations tested by different models. Model 1: age-related effects on inhibitory control (regardless of incentive condition). Model 2: age by trial type interactions (the "reward boost"). Model 3: age-related effects on basal ganglia tissue iron. Model 4: main effects of tissue iron on inhibitory control. Model 5: tissue iron by trial type interactions on inhibitory control. Model 6: three-way interactions between tissue iron, trial type, and age on inhibitory control performance based on the hypothesis that reward-related DAergic function will have a unique reward-boosting effect on inhibitory control in adolescence.

$$Model\ 1 = correct\ response\ rate \sim trial\ type + sex + s(age,\ k = 4,\ fx = T),\ random = list(ID =\sim 1) \tag{1}$$

2.6.3. Characterizing age-related trends in antisaccade performance

GAMMs were chosen for age-related analyses based on theorized non-linear trajectories of AS development (Shulman et al., 2016) that are supported by previous findings using this task (Luna et al., 2004; Ordaz et al., 2013). To characterize developmental trajectories in antisaccade performance, we implemented GAMMs that included random intercepts estimated for each participant. Penalized thin plate regression splines were implemented (maximum degrees of freedom for the smooth term was 3 ($k - 1$, $k = 4$ knots)) to assess linear and non-linear age effects (Marra and Wood, 2011; Wood, 2004). Four knots were chosen, consistent with prior neuroimaging studies utilizing GAMM models in adolescent populations (Gracia-Tabuenca et al., 2021; Larsen et al., 2020a; Pehlivanova et al., 2018; Pines et al., 2021; Van Duijvenvoorde et al., 2019; Xia et al., 2018) based on the expectation that there are unlikely to be more than three resolvable inflection points, and to avoid overfitting the data, thus providing a form of model regularization. We first tested for significant age by trial type interactions (reward and neutral; factor-smooth interactions; see Model 2) and used a parametric bootstrap likelihood function (using 1000 draws) as a model comparison procedure to test that the interaction model was a significant improvement on the main effect model (regardless of trial type, see Model 1). If the interaction term was not significant and/or the main effect model was the superior model, trial type was modelled as a covariate and main effects of age are presented. To assess age-ranges of significant change, we calculated the first derivative of the smooth function of age from the GAMM model using finite differences (as were conducted in Larsen et al., 2020a), and 95% confidence intervals of the derivatives were generated (*gratia* package in R (Simpson, 2018)). In the case that the confidence interval of the derivative did not include zero, this indicated intervals of significant change. We also tested for sex by age interactions, and this interaction term was not significant in any model, thus we removed the interaction term and modeled sex as a covariate.

2.6.4. Characterizing age-related trends in the reward enhancement to antisaccade performance

To further characterize the age at which rewards elicit a significant improvement to antisaccade performance (i.e., how long the 'reward boost' persisted), in the cases where we observed significant interactions between age and trial type (above), we calculated the difference smooth between each level of trial type (*mgcv* package in R (Simpson, 2017). This tests the age interval at which the slope is significantly different

across trial types (essentially the derivative of the *difference* smooth), and significant periods were identified where the confidence interval did not include zero.

2.6.5. Characterizing age-related trends in tissue iron

To characterize developmental trajectories in tissue iron, we implemented GAMMS (GAMMs) separately across each basal ganglia region of interest (ROI), including random intercepts estimated for each participant. As with the AS analyses, regression splines were implemented (maximum of 4 degrees of freedom) to assess linear and non-linear age effects. We first tested for significant age by sex interactions (factor-smooth interactions) and used a parametric bootstrap likelihood function (using 1000 draws) as a model comparison procedure to test that the interaction model was a significant improvement on the main effect model (regardless of sex). As the interaction term was not significant and the main effect model was the superior model, sex was modelled as a covariate and main effects of age are presented (see Model 3). We additionally modelled mean frame displacement (FD) as a motion estimate. For this analysis, data were considered significant at $p = .01$ to account for multiple comparisons across the 4 ROIs (Bonferroni correction:.05/4 ROIs, corrected alpha =0.0125).

$$Model\ 3 = nT2w \sim sex + FD + s(age,\ k = 4, fx = T),\ random = list(ID =\sim 1) \tag{3}$$

2.6.6. Characterizing the Relationship between Tissue Iron and Antisaccade Performance

We next investigated the relationship between estimates of nT2*w on antisaccade performance using GAMMs, including random intercepts estimated for each participant and modeling age as a smoothed term as above. We first tested for significant main effects of nT2*w (Model 4), and next tested for nT2*w by trial type interactions (Model 5), and this interaction term was removed if not significant and main effects are

$$Model\ 2 = correct\ response\ rate \sim trial\ type + sex + s(age,\ k = 4,\ fx = T) + s(age,\ by = trial\ type,\ k = 4,\ fx = T),\ random = list(ID =\sim 1) \tag{2}$$

presented with trial type modeled as a covariate (Model 4). We tested for nT2*w by region of interest (ROI) interactions, in addition to nT2*w by sex interactions, and these interaction terms were not significant, thus they were removed and sex and ROI were modelled as covariates, in addition to mean frame displacement (FD) as a motion estimate.

$$Model\ 4 = correct\ response\ rate \sim nT2w + trial\ type + sex + ROI + FD + s(age,\ k = 4,\ fx = T),\ random = list(ID =\sim 1) \tag{4}$$

$$Model\ 5 = correct\ response\ rate \sim nT2w * trial\ type + sex + ROI + FD + s(age,\ k = 4,\ fx = T),\ random = list(ID =\sim 1) \tag{5}$$

2.6.7. Characterizing whether the relationship between tissue iron and antisaccade performance changed with age

To investigate whether the relationship between nT2*w and performance changed with age, as we might expect should nT2*w play a larger role in the reward enhancement that is most prominent during adolescence, we used linear mixed effects models (*lme4* package; Bates et al., 2014; R version 3.5.2 via RStudio version 1.1.463; https://www.r-project.org/) to test for three-way interactions between nT2*w, trial type and age^{-1}, modelling sex and motion as covariates (Model 6). Age^{-1} (inverse) was used as opposed to linear age as model testing procedures revealed that age^{-1} had the lower Akaike Information Criterion (AIC), indicating best model fit.

high intraclass correlation coefficients (ICCs, Psych package, ver 2.1.6, Revelle, 2022) in basal ganglia nT2*w values across visits (raw values: mean nT2*w across ROIs: ICC = .83, $F = 15.57$, $p < .001$; NAcc: ICC = .85, $F = 18.25$, $p < .001$; Putamen: ICC = .79, $F = 12.59$, $p < .001$; Caudate: ICC = .61, $F = 5.70$, $p < .001$; Pallidum: ICC = .83, $F = 15.92$, $p < .001$). Additionally, membership in the nT2*w groups (high/low) was longitudinally stable, evidenced by high ICCs in the age-residualized estimates for mean nT2*w across ROIs that were used to separate individuals into groups (ICC = .81, $F = 13.97$, $p < .001$), in addition to only 11/122 (9%) participants switching from one group to another across visits.

$$Model\ 6 = correct\ response\ rate \sim nT2w * trial\ type * age^{-1} + sex + ROI + FD,\ random = list(ID = \sim 1) \tag{6}$$

To characterize the nature of significant three-way interactions, we separated individuals into two groups reflecting *high* and *low* nT2*w values relative to one's age. Age-residualized estimates were obtained by regressing age from the mean nT2*w value across ROIs using GAMMs with nT2*w as the dependent variable and age as the fixed effects factor (Larsen et al., 2020b). The residuals of this model were then used to separate individuals into *high* (residuals of < 0, n = 97 sessions) and *low* (residuals of $>= 0$, n = 91 sessions) tissue iron groups relative to their age. Next, we repeated the GAMM analyses detailed above (Model 2) to investigate age by trial type interactions within each nT2*w group. Importantly, nT2*w estimates were longitudinally stable, evidenced by

3. Results

3.1. Antisaccade correct response rate and development

3.1.1. Modulation of antisaccade correct response rate by rewards

In line with prior literature showing an enhancing effect of incentives on AS performance, we observed a significant main effect of trial type on AS correct response rate ($\beta = .47$, $t = 5.67$, $p < .001$, *Model 1*), with higher rates in the rewarded trials (mean = .80, SE ±.01) relative to neutral (mean = .74, SE ±.01). We also observed a significant main effect of reward on correct response latency ($\beta = -.20$, $t = -2.68$, $p = .008$), with lower latencies in the rewarded trials (mean = 317 ms, SE ± 3.57 ms) relative to neutral (mean = 327 ms, ± SE 3.47 ms), and
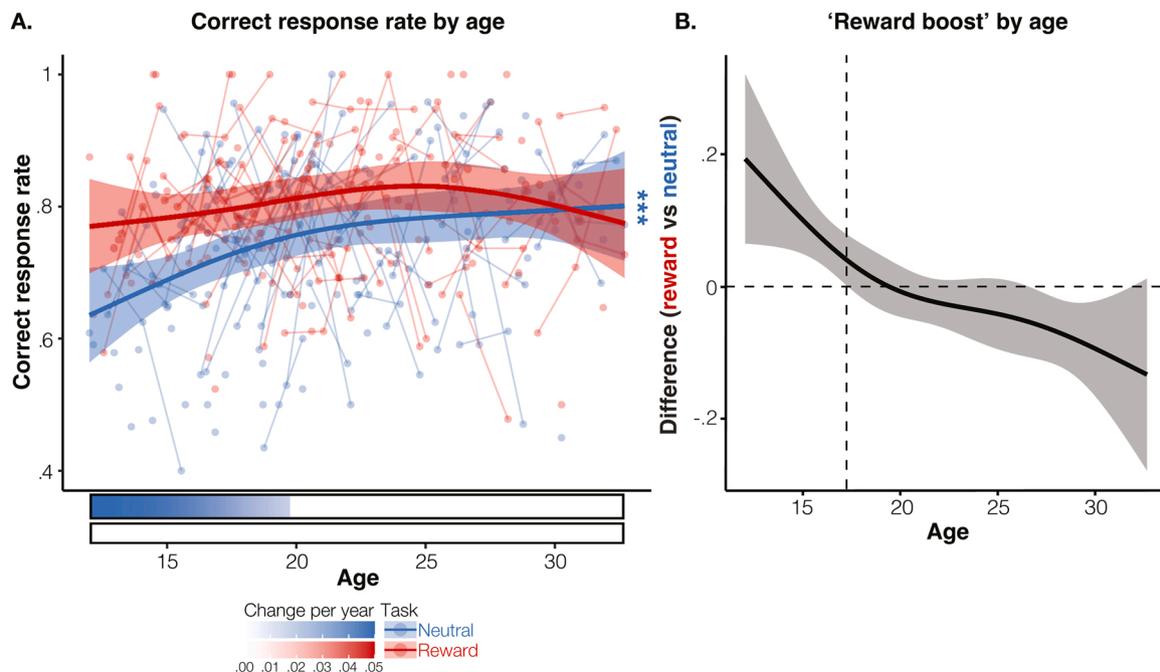
Fig. 3. Development of antisaccade correct response rate through adolescence across trial types. (A) Age-related trajectories for antisaccade correct response rate are presented for reward trials (red) and neutral trials (blue). Statistical values reflect smoothed terms for age (s(age)) using general additive mixed models (GAMMs). Beneath each plot, colored bars show the age range where the derivative of the fitted smooth function was significant for each trial type reflecting significant age-related improvements, with the intensity of the color reflecting the value of the derivative in units of change per year. (B) Difference in the smoothed terms for age across reward and neutral trials are plotted and give an index of the 'reward boost'. Periods where the confidence interval does not overlap with 0 reflect the age range at which the slope differed significantly across trial types. In (A), individual datapoints reflect values for each session, and connected lines reflect sessions from the same participants (all available data for each participant across all visits is included, n = 193 sessions). * p < .05, * * p < .01, * * * p < .001.

A. nT2*w values across regions

B. nT2*w values by age
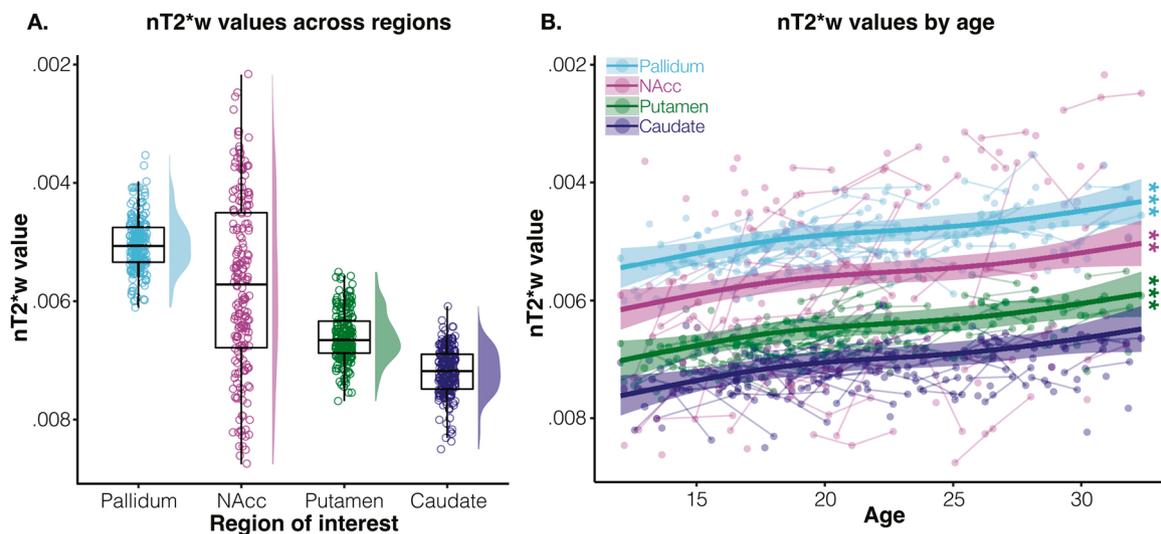
Fig. 4. Tissue iron (nT2 *w values) distributions and age effects across basal ganglia regions of interest. (A) Distributions of nT2*w values are presented for each basal ganglia region of interest. (B) Age-related trajectories for nT2*w values are shown for each region of interest. Statistical values reflect smoothed terms for age (s (age)) using general additive mixed models (GAMMs). In (A) and (B), for ease of interpretation, the y-axis is reversed to reflect the inverse relationship between nT2*w values and tissue iron, and individual datapoints reflect nT2*w values for each session. Connected lines in (B) reflect sessions from the same participants (all available data for each participant across all visits is included, n = 188 sessions). P values are Bonferroni corrected. * p < .05, * * p < .01, * ** p < .001.

standard deviation in latencies ($\beta = -.25$, $t = -2.66$, $p = .008$), with lower SD in the rewarded trials (mean = 81.1 ms, SE $\pm$ 2.28 ms) relative to neutral (mean = 90.7, SE $\pm$ 3.15 ms). Latency results for all further analyses are shown in the Supplementary Section.

3.1.2. Neutral trial antisaccade correct response rate improves with age

In order to test the primary hypothesis that age-related AS trajectories would differ as a function of reward contingency, we tested for age by trial type interactions (i.e., factor-smooth interactions using GAMMs, see Methods and *Model 2*), and further examined age-related changes in each condition Although AS correct response rate (overall, main effect model) improved into adulthood ($F = 4.85$, $p = .003$, *Model 1*), we importantly observed a significant age by trial type interaction ($F = 2.98$, $p = .03$, *Model 2*) that was a significant improvement on the main effect model (see Methods). Neutral trial correct response rate improved with increasing age ($F = 6.07$, $p < .001$; Fig. 3A), and analysis of the derivatives of the fitted age trajectories (see Methods) identified a significant period of increase between the youngest age of 12.04 and 19.71 years, while reward trial correct response rate did not show a significant effect of age ($F = 1.13$, $p = .34$; Fig. 3A). There were no significant age by sex interactions or three-way interactions between age, sex, and trial type ($p < .05$).

3.1.3. Enhancing effects of rewards on antisaccade correct response rate decrease with age

To understand how long the 'reward boost' persisted, we calculated differences in the smoothed terms for age between each level of trial type (see Methods and *Model 2*). These analyses show that the slopes significantly differed across trial types early- to mid- adolescence, persisting until approximately 17 years of age, after which this effect was diminished (Fig. 3B), indicating that the 'reward boost' was most prominent early- to mid- adolescence.

3.2. Tissue iron data

### 3.2.1. Age-related changes in tissue iron concentrations

nT2 *w values were extracted separately across each basal ganglia region of interest (ROI; Fig. 4A), and are consistent with distributions and developmental trajectories found in prior studies of tissue iron (Larsen et al., 2020a; Peterson et al., 2019; Price et al., 2021) using more

direct measures obtained using R2' (Larsen et al., 2020b; Parr et al., 2021), R2* (Larsen et al., 2020a) and quantitative susceptibility mapping (QSM; Haacke et al., 2010, 2005; Peterson et al., 2019). nT2*w values were extracted separately across each ROI in order to examine the specificity the relationship with AS performance in individual subregions. Note that tissue iron is inversely related to T2* , therefore for ease of interpretation, nT2*w values in all figures have been reversed such that negative values reflect high tissue iron and positive values reflect low, indirectly reflecting increased and decreased indices of DA-related neurophysiology, respectively (Larsen et al., 2020b).

As in the AS task performance, GAMMs were utilized to characterize non-linear effects in tissue iron developmental trajectories (see Methods). As has previously been shown (Larsen et al., 2020a, 2020b; Larsen and Luna, 2015; Peterson et al., 2019), tissue iron robustly increased with age in each ROI (Fig. 4B, *Model 3*) including the pallidum ($F = 19.48$, $p < .001$, $p_{Bonferroni} < 0.001$), the nucleus accumbens (NAcc; $F = 6.36$, $p < .001$, $p_{Bonferroni} = 0.002$), and the putamen ($F = 21.42$, $p < .001$, $p_{Bonferroni} < 0.001$), though increases in the caudate nucleus were not significant ($F = 1.36$, $p = .25$, $p_{Bonferroni} = 1.00$). There were no significant age by sex interactions. nT2 *w values were included in the behavioral analysis detailed below as an index of basal ganglia dopamine neurobiology.

3.2.2. Associations between antisaccade correct response rate and tissue iron

In order to test the hypothesis that tissue iron, reflecting DA-related basal ganglia neurophysiology, contributed to AS performance, particularly in reward trials, we tested for interactions between tissue iron and trial type (see Methods), and further examined the relationship between tissue iron and performance in each condition. We did not observe a significant main effect of tissue iron on correct response rate (overall; Fig. S2A; $\beta = -.03$, $t = -1.01$, $p = .31$, *Model 4*), or a significant interaction between tissue iron and trial type ($\beta = .02$, $t = 0.57$, $p = .57$, *Model 5,* though *Model 4* was the superior model). Given the significant age by trial type interaction in the behavioral data, we performed exploratory follow-up tests, which revealed a non-significant effect of tissue iron in the reward trial condition (Fig. S2A; $\beta = -.02$, $t = -0.73$, $p = .47$) and in the neutral trial condition (Fig. S2A; $\beta = -.03$, $t = -0.84$, $p = .40$). We did not observe significant interactions with ROI (all $p < .05$), and the interaction term was therefore removed and
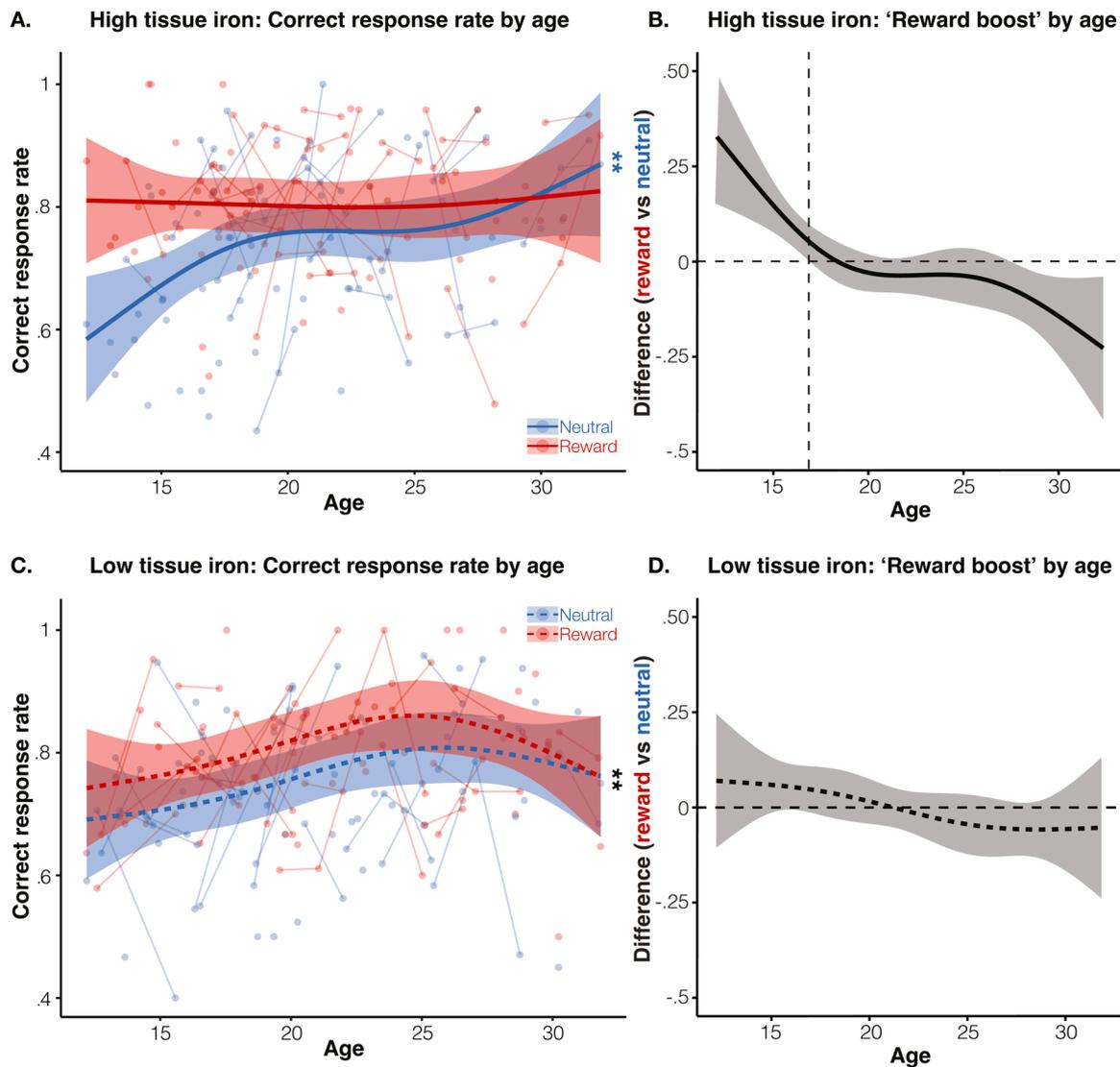
Fig. 5. Development of antisaccade correct response rate through adolescence in high and low tissue iron groups. (A) Age-related trajectories for antisaccade correct response rate for reward trials (red) and neutral trials (blue) in the high tissue iron group (relative to age). (B) Difference in the smoothed terms for age across reward and neutral trials are plotted for the high tissue iron group. (C) Age-related trajectories for antisaccade correct response rate for reward trials (red) and neutral trials (blue) in the low tissue iron group (relative to age). (D) Difference in the smoothed terms for age across reward and neutral trials are plotted for the low tissue iron group. In (A) and (C), individual datapoints reflect values for each session, and connected lines reflect sessions from the same participants (all available data for each participant across all visits is included. High tissue iron group: n = 97 sessions; low tissue iron group: n = 91 sessions). Statistical values reflect smoothed terms for age (s(age)) using general additive mixed models (GAMMs). In (B) and (D), periods where the confidence interval does not overlap with 0 reflect the age range at which the slope differed significantly across trial type. Colored symbols denote significance levels within each trial type, while black symbols denote significant main effects (independent of trial type). * p < .05, * * p < .01, * ** p < .001.

modelled as a covariate (see Supplement for interaction effects across each ROI).

3.2.3. Associations between antisaccade correct response rate, tissue iron, and age

To investigate whether the relationship between tissue iron and correct response rate changed with age, as we hypothesized that tissue iron, via it's link with DA, should play a larger role in the reward enhancement that is most prominent during early- to mid- adolescence, we tested for three-way interactions between tissue iron, trial type, and inverse age (age^{-1};see Methods and *Model 6*). Critically, we observed a significant three-way interaction between tissue iron, trial type, and age^{-1} on correct response rate ($\beta = -.08$, $t = -2.35$, $p = .02$, *Model 6*).

To characterize the nature of this interaction, we separated individuals into two groups reflecting *high* (n = 97) and *low* (n = 91) tissue iron values (relative to one's age, which was longitudinally stable for

each group, see Methods) and repeated the GAMM analyses detailed above to investigate age by trial type interactions within each tissue iron group. In the high tissue iron group, we observed a significant main effect of trial type (trial type – neutral vs reward) on AS correct response rate ($\beta =.48$, $t = 4.47$, $p < .001$, *Model 1*), with higher rates in rewarded trials (mean =0.80, SE ±.01) relative to neutral (mean =0.74, SE ±.01). While we did not observe a significant main effect of age on AS correct response rate (overall; $F = 1.91$, $p = .13$, *Model 1*), importantly, we observed a significant age by trial type interaction ($F = 5.17$, $p = .002$, *Model 2*) that was a significant improvement on the main effect model (see Methods). Neutral trial correct response rate improved with increasing age (Fig. 5A; $F = 5.12$, $p = .003$), and reward trial correct response rate did not show a significant effect of age (Fig. 5A; $F =0.07$, $p = .98$). There were no significant age by sex interactions or three-way interactions between age, sex, and trial type (all $p > .05$). Differences in the smoothed terms for age across reward and neutral trial conditions

revealed that the enhancing effects of rewards were most pronounced in adolescence in the high tissue iron group, persisting until approximately 17 years of age, after which this effect was diminished (Fig. 5B).

By comparison, in the low tissue iron group, we observed a significant main effect of trial type (neutral vs reward) on AS correct response rate ($\beta = .43$ $t = 3.48$, $p < .001$, *Model 1*), with higher rates in rewarded trials (mean $=0.79$, $\pm.01$) relative to neutral (mean $=0.74$, $\pm.01$). However, here we observed a significant main effect of age on correct response rate (overall; Fig. 5C; $F = 4.13$, $p = .007$, *Model 1*), but no significant age by trial type interaction ($F = 0.39$, $p = .76$, *Model 2*), indicating comparable developmental trajectories in both reward ($F = 2.94$, $p = .04$) and neutral trials ($F = 1.98$, $p = .12$) (i.e., diminished reward boost), and the main effect model was a significant improvement on the interaction model (see Methods). There were no significant age by sex interactions or three-way interactions between age, sex, and trial type (all $p > .05$). Finally, differences in the smoothed terms for age across reward and neutral trial conditions revealed that the enhancing effects of rewards did not change with age in the low tissue iron group (confidence intervals fully overlap with 0; Fig. 5D).

4. Discussion

In this study, we used longitudinal MR-based assessments of basal ganglia tissue iron to characterize the role of DA-related neurobiology in the enhancement of adolescent inhibitory control by reward incentives ('reward boost'). We characterized age-related trajectories of inhibitory control during an antisaccade (AS) task with both reward and neutral trials and explored whether basal ganglia tissue iron supported the reward boost that is most prominent in early- to mid- adolescence. As expected, we found that, neutral trial performance improved from adolescence into adulthood, while reward trial performance, even in early adolescence, approximated that of adults (Fig. 3A). This reward boost decreased into adulthood as neutral performance and reward performance converged (Fig. 3B). Further, we found that tissue iron concentration was associated with individual differences in the degree of the reward enhancement, specifically in adolescence (Fig. 5), where adolescents with relatively high levels of tissue iron had a greater reward boost (Fig. 5A & B) compared to low (Fig. 5C & D). To our knowledge, this is the first study demonstrating that tissue iron properties linked to DA physiology contribute to the modulation of inhibitory control by reward incentives developmentally.

As has been shown in prior studies assessing inhibitory control (Alahyane et al., 2014; Fischer et al., 1997; Klein and Foerster, 2001; Levin et al., 1991; Liston et al., 2006; Luna et al., 2004; Munoz et al., 1998; Ordaz et al., 2013; Ridderinkhof and van der Molen, 1997; Williams et al., 1999), AS performance in neutral trials showed protracted maturation during the adolescence until approximately 20 years of age, with age-related increases in correct response rate (Fig. 3A). These results are consistent with neurodevelopmental models suggesting that ongoing maturation of executive systems (Luna and Wright, 2016; Steinberg, 2004) may underlie the ability to suppress task-irrelevant signals in a sustained fashion. Consistent with previous findings (Duka and Lupp, 1997; Geier et al., 2010; Geier and Luna, 2012; Hallquist et al., 2018; Hardin et al., 2007; Hawes et al., 2017; Jazbec et al., 2006, 2005; Luna et al., 2013; Padmanabhan et al., 2011; Paulsen et al., 2015; Zhai et al., 2015), incentives enhanced inhibitory control performance, evidenced by higher correct response rates (Fig. 3A) relative to the neutral condition. We extend these findings by characterizing the significant developmental period of this effect, which is predominant in adolescence until approximately 17 years of age (Fig. 3B). These findings provide support for a model in which adult levels of cognitive control are available, but unreliable in adolescence (Luna et al., 2015; Luna and Wright, 2016; Shulman et al., 2016), potentially requiring greater effort or motivation, which can be facilitated by engaging DAergic-mediated reward processes. The age-specificity of this effect, evidenced by both a significant age by incentive interaction and the

difference in developmental trajectories between incentive conditions (Fig. 3B), suggests that adolescents may be particularly sensitive to the enhancing effects of rewards, in line with previous findings in adolescent cognitive control (Geier et al., 2010; Insel et al., 2019, 2017; Padmanabhan et al., 2011; Teslovich et al., 2014; Van Duijvenvoorde et al., 2016 but see Rodman et al., 2021 who showed that rewards similarly modulated effort in adolescents and adults during a physical force task). This increased reward sensitivity may be driven by developmental changes within the Daergic system during adolescence (Andersen et al., 1997; Luciana et al., 2012; Padmanabhan and Luna, 2014; Wahlstrom et al., 2010) and increased reward drive (i.e., increased motivation when rewards are at stake) that facilitates exploration and experience-dependent plasticity (Luciana et al., 2012), required for specialization of frontostriatal circuits and refinements in cognitive processes into adulthood. Pubertal maturation, which contributes to DAergic changes in adolescence (Kuhn et al., 2010; Ladouceur et al., 2019; Sárvári et al., 2014; Sisk and Foster, 2004; Sisk and Zehr, 2005) and the development of inhibitory control networks (Bramen et al., 2012, 2011; Constantinidis and Luna, 2019; Goddings et al., 2014; Herting et al., 2015, 2012; Neufang et al., 2009; Nguyen et al., 2013; Peper et al., 2012), may also partially contribute to the observed relationship between DA-related neurophysiology and AS performance in adolescence. Although we do not address the role of puberty here, previous findings have shown that age-related improvements in AS performance (in a non-rewarded context) are relatively independent of pubertal stage and pubertal hormones in adolescence (Ordaz et al., 2018), though *rewarded* AS performance was not assessed and may have important associations with pubertal timing. Given sex differences in the timing of puberty (Constantinidis and Luna, 2019), such differences may suggest a role for pubertal hormones, however, such differences and sex by age interactions were notably absent in the current study and in previous studies using the AS (Ordaz et al., 2013). Regardless, it remains possible that pubertal maturation may contribute to individual differences in rewarded AS performance in adolescence, potentially via individual differences in DAergic processes, representing an exciting avenue for future research. Future studies will apply comprehensive models to investigate pubertal timing and its association with reward systems through adolescence.

The mechanisms underlying the developmental differences in the effects of rewards on inhibitory control remain unclear. Given adolescent increases in nucleus accumbens (NAcc) reward-related BOLD activation during both the rewarded AS (Geier et al., 2010; Padmanabhan et al., 2011; Paulsen et al., 2015a) and decision-making tasks (Ernst et al., 2005; Galvan et al., 2006; Luna et al., 2013; Van Leijenhorst et al., 2010), and the DAergic physiology of the NAcc with projections originating from the ventral tegmental area (VTA) (Kelley and Berridge, 2002; Schultz, 2002; Wise, 2004), DAergic processes may support enhanced performance in adolescence. Converging evidence in animal models suggest that DA levels increase during adolescence (Kalsbeek et al., 1988; Meng et al., 1999; Rosenberg and Lewis, 1994, 1995b; Seeman et al., 1987; Spear, 2000; Wahlstrom et al., 2010), including activity of DA neurons in the midbrain (McCutcheon et al., 2009), tonic DA peaks in striatum (Andersen et al., 2002) and heightened DA innervation of the PFC (Benes et al., 2000; Lambe et al., 2000; Lewis et al., 2002, 1995; Rosenberg and Lewis, 1994,1995a,1995b), which may uniquely drive activity within inhibitory control circuits (Geier et al., 2010; Hallquist et al., 2018; Padmanabhan et al., 2011), and/or lead to a greater motivation to obtain rewards in adolescents relative to adults. In line with the Driven Dual Systems model (Luna and Wright, 2016; Shulman et al., 2016), while prefrontal cortical circuits are available but unstable and unreliable by adolescence, a relative predominance of striatal systems may drive these circuits to perform in a more consistent fashion in service of obtaining rewards. This is supported by earlier findings showing that this reward boost is supported by increased NAcc activation (Geier et al., 2010; Hallquist et al., 2018; Padmanabhan et al., 2011), as well as cognitive control regions

including frontal and parietal eye fields, the anterior cingulate cortex, and ventromedial prefrontal cortex (Geier et al., 2010; Hallquist et al., 2018; Padmanabhan et al., 2011), and increased task-related connectivity across salience networks in adolescents compared to adults (Hallquist et al., 2018). In adults, AS performance has reached optimal levels and stabilizes, accompanied by refinement and specialization across inhibitory control circuits (Geier et al., 2010; Hallquist et al., 2018), at which point incentives may no longer be required to enhance ceiling-level performance. Thus, increased recruitment of the basal ganglia in adolescence in response to incentives may drive activity in oculomotor and cognitive control regions needed to execute the response that will result in a reward, which in this case, is the difficult task of inhibitory control.

Given the lack of in vivo measures to assess DA function in human pediatric populations, the role of DAergic processes in facilitating improvements in adolescent inhibitory control is poorly understood. Novel to this study, we show that the enhancing properties of rewards are unique to adolescence and vary with differing baseline levels of basal ganglia DA-related physiology. Specifically, we find that tissue iron is more strongly related to the reward boost in adolescence (Fig. 5), until approximately 17 years of age, as was expected given that the reward boost was predominant in adolescence (Fig. 3B). Importantly, the effects of tissue iron differed across incentive conditions, with greater correspondence between tissue iron and rewarded AS performance as compared to neutral. This apparent specificity of tissue iron to rewarded AS performance is critical because it demonstrates that individual differences in basal ganglia DA-related neurobiology support the ability for reward to enhance inhibitory control, rather than modulating inhibitory control more generally (in neutral trials). In further support of this notion, we found differing developmental trajectories among individuals with high and low tissue iron depending on incentive condition: whereas individuals with high tissue iron showed the reward boost, driven by adult-like levels of inhibitory control in the reward condition, but still immature neutral trial performance that continued to improve through adolescence (Fig. 5A & B), the reward boost was relatively diminished in individuals with low tissue iron (Fig. 5C & D), who had comparable developmental trajectories in performance regardless of trial condition (i.e., an absence of the reward boost as reward trial performance continued to mature on par with neutral performance). These results are consistent with literature suggesting that individual differences in motivated cognitive control (i.e., in the presence of rewards) are mediated by DAergic processes (Cools, 2019), which may be reflected here as individual differences in basal ganglia tissue iron properties. These differences may be trait related and have implications for neurodevelopmental models of reward processing in adolescence that assume that adolescents as a group have heightened reward reactivity. Specifically, our results suggest that relatively higher levels of DA availability in adolescence may potentiate the effect of incentives on inhibitory control (to a greater extent than in adulthood), potentially by enhancing activity in and/or connectivity between inhibitory control networks. Despite our initial hypothesis that tissue iron within individual subregions of the basal ganglia may differentially contribute to the reward boost in adolescence, we found that the relationship between tissue iron and the reward boost was similar across basal ganglia ROIs. Tissue iron estimates across individual ROIs were generally well correlated, as reflected by the lack of differences among regions in predicting performance, suggesting that maturation of basal ganglia DA systems as a whole is relevant to the development of reward-related behaviors examined here. Differences among regions may be more apparent when considering the specific functional properties of those regions, such as BOLD activation and/or connectivity, which is an exciting opportunity for future work.

These findings are consistent with broader literature showing that appetitive motivation (i.e., through exogenous rewards) can enhance cognitive control (Aarts et al., 2011; Cools, 2011), and are in support of studies in healthy adults that have shown that individual differences in

striatal DA, including DA synthesis capacity (Aarts et al., 2014, 2011; Hofmans et al., 2020; Westbrook et al., 2020) and DA transporter genes (Aarts et al., 2014), promote the motivational effects of reward on cognitive control. One possibility is that variability in DAergic processes may modulate the *willingness* (i.e., the subjective value of cognitive 'work') to expend cognitive effort, rather than the *ability* to exert cognitive control (Aarts et al., 2014; Cools, 2019; Hofmans et al., 2020; McGuigan et al., 2019; Westbrook et al., 2020). For example, Westbrook et al. (2020) showed that individuals with higher striatal DA synthesis capacity were more willing to expend cognitive effort in the presence of rewards during an N-back working memory task (Westbrook et al., 2020), and further showed that increased DA synthesis capacity magnified the weight of the benefits on choice (versus the costs, i.e., effort). Our results are in support of these findings and may suggest that adolescents with high tissue iron indices, reflecting higher DA availability, may have been more motivated to engage cognitive control in order to obtain rewards. Furthermore, the relative lack of tissue iron modulation of neutral trial performance is in further support for the hypothesis that basal ganglia DA may not modulate the *ability* to exert cognitive control per se (Cools, 2019; Westbrook et al., 2020) but rather perhaps the *willingness* and/or the motivation that can be amplified by incentives. While adolescents may not *deliberatively* be less willing to engage optimal executive performance in neutral trials, our results suggest that rewards can stimulate greater effort to execute reliable executive responses.

These findings are also in agreement with literature suggesting that the effects of DA on cognition depend on baseline striatal and prefrontal DA levels (Arnsten and Goldman-Rakic, 1998; Cools et al., 2009; Cools and D'Esposito, 2011; Williams and Goldman-Rakic, 1995; Yerkes and Dodson, 1908). However, perhaps counterintuitive to the broader literature showing that individuals with high DA indices may in fact experience a *detriment* to cognitive function (i.e., working memory (Arnsten and Goldman-Rakic, 1998; Cools and D'Esposito, 2011; Williams and Goldman-Rakic, 1995), and reversal learning (Cools et al., 2009)) with greater DA signaling, our findings should be conceptualized in a neurodevelopmental context. This result was relatively specific to adolescence, when DAergic processes, including DA availability potentially reflected in tissue iron properties, are still undergoing developmental changes and have not yet reached adult levels (L.P. Spear, 2000a, 2000b; Wahlstrom et al., 2010). Our results suggest that adolescents with relatively higher tissue iron levels, in part, reflecting DA availability, may have the opportunity to recruit striatal systems to a greater degree where they can push executive systems to work at optimal levels in the service of reward receipt. Adolescents with lower levels of tissue iron may be limited in their ability to engage relevant systems to affect behavior, and may require a greater degree of reward stimulation (in a dose-dependent manner) to engage striatal DA-mediated processes. Differences in tissue iron in adolescence may also reflect different maturational timelines, with those with higher levels possibly having earlier maturation of the DAergic system, and thus the ability to leverage it to support cognitive control.

In terms of the mechanisms through which DA-related basal ganglia neurobiology may affect the modulation of inhibitory control by rewards, PET studies in adults have shown that striatal DA, specifically synthesis capacity measured using 6-[^{18}F]fluro-L-m-tyrosine (FMT), predicts performance on prefrontal-dependent tasks, including working memory (Cools et al., 2008; Landau et al., 2009), in addition to the magnitude of activation within prefrontal regions (Landau et al., 2009). DA innervates multiple frontostriatal circuits, including those responsible for motor, cognitive, and motivational aspects of behavior (Alexander et al., 1991, 1986; Cools, 2019). Classic models of basal ganglia function (and gating models for motor selection; Gurney et al., 2001a, 2001b) suggest that DA regulates the flexible gating of cognitive actions by increasing activity in the direct (aka "Go") pathway, and decreasing activity of the indirect (aka "No-go") pathway in accordance with a top-down "behavioral relevance signal" (i.e., don't look at the stimulus;

Munoz and Everling, 2004). Likewise, a role for the basal ganglia DA has been shown in modulating connectivity from prefrontal cortices (which provide task-relevant information) to sensory, motor, and association cortices (van Schouwenburg et al., 2015, 2010), specifically amplifying and inhibiting task-relevant and irrelevant signals, respectively. During adolescence, frontostriatal connectivity continues to undergo maturational changes (Christakou et al., 2011; Fareri et al., 2015; Insel et al., 2017; Parr et al., 2021; van den Bos et al., 2015; Van Den Bos et al., 2012; Vink et al., 2014), potentially contributing to an inability to inhibit task irrelevant signals leading to limited neutral trial performance. Indeed, decreased task-related frontostriatal functional connectivity has been shown to underlie limited inhibitory control performance in adolescence, increasing into adulthood (Vink et al., 2014). However, incentives have been shown to enhance activation (Geier et al., 2010; Hawes et al., 2017; Padmanabhan et al., 2011) and connectivity (Hallquist et al., 2018) across cognitive control networks during the AS task in adolescence, which may facilitate the reward boost to inhibitory control by amplifying task-relevant signals. It is possible that enhanced basal ganglia DA-related function in adolescence may facilitate improvements in inhibitory control by enhancing connectivity between relevant cognitive control networks, resulting in greater modulation of prefrontal cortical regions. Although this hypothesis remains untested, we have recently shown that individual differences in NAcc tissue iron are related to the strength of reward-state frontostriatal connectivity in adolescence, and that developmental differences in tissue iron are predictive of longitudinal decreases in frontostriatal connectivity (Parr et al., 2021). This finding illustrates the potential for basal ganglia tissue iron to modulate connectivity in adolescence, which may provide a mechanism underlying the ability for rewards to enhance AS performance during this period.

Though non-invasive in vivo markers of the human mesolimbic DA system have been utilized in developmental research, these studies have mainly focused on striatal and midbrain BOLD activation as an indirect proxy for DA function and a marker of adolescent reward sensitivity (Bjork et al., 2010, 2004; Braams et al., 2015; Ernst et al., 2005; Galvan et al., 2006; Geier et al., 2010; Luna et al., 2013; Padmanabhan et al., 2011; Paulsen et al., 2015). However, the relationship between the BOLD response and DA physiology remains unclear (Attwell and Iadecola, 2002; Brocka et al., 2018; Logothetis, 2003; Logothetis and Wandell, 2004). Tissue iron has influence on the T2* signal, and has been quantified using a variety of relaxometry-based MR measures including R2* (Haacke et al., 2010; Larsen et al., 2020a), R2' (Larsen et al., 2020b; Sedlacik et al., 2014), susceptibility-based approaches (Haacke et al., 2004; Peterson et al., 2019), and nT2*w imaging (Larsen and Luna, 2015; Peterson et al., 2019; Price et al., 2021). nT2*w imaging in particular represents a promising, non-invasive, indirect measure of basal ganglia DA-related neurophysiology, as it can be readily obtained using existing T2* -weighted echo planar imaging (EPI) scans acquired during most fMRI protocols. nT2*w imaging has been used to characterize age-related changes in basal-ganglia iron concentration through adolescence (Larsen and Luna, 2015; Peterson et al., 2019), consistent with age-related trends observed in the current study, and with previously published maturational trajectories using other, well-validated, measures of tissue iron (Hallgren and Sourander, 1958; Hect et al., 2018; Larsen et al., 2020b, 2020a; Peterson et al., 2019). Furthermore, the development of basal ganglia tissue iron concentration proceeds similarly to animal studies of DA concentration, increasing through adolescence and stabilizing into adulthood (Hallgren and Sourander, 1958; Larsen et al., 2020a, 2020b; Larsen and Luna, 2015; Peterson et al., 2019). It should be noted that T2* -based tissue iron imaging methods are also sensitive to hypointensities due to myelin concentration (Aoki et al., 1989; Chavhan et al., 2009). However, myelin is diamagnetic, and tissue iron is paramagnetic, and therefore has a greater impact on the T2* signal, causing more substantial hypointensities in iron-rich areas such as the basal ganglia relative to other areas of the brain (Colcombe et al., 2019; Langkammer et al., 2010; Larsen and Luna,

2015; Schenck, 2003). Furthermore, studies have shown that associations between age and T2* are predominant in the basal ganglia and midbrain relative to cortical areas and white matter tracts, indicating that developmental changes in T2* -based indices of basal ganglia neurophysiology are likely to reflect developmental differences in tissue-iron concentrations (Larsen and Luna, 2015; Peterson et al., 2019). Thus non-invasive measures of tissue iron, indirectly reflecting DA-related basal ganglia neurophysiology (Larsen et al., 2020b, 2020a; Parr et al., 2021), can bridge a critical gap in understanding how individual differences in DAergic mechanisms contribute to trajectories in human neurocognitive development.

5. Conclusions

This study provides novel in vivo human evidence that DA-related neurophysiology within the basal ganglia is undergoing unique maturation during adolescence, supporting the ability to execute responses that lead to reward receipt, including inhibitory control. Individual differences in basal ganglia neurophysiology in adolescence may be reflective of maturational timing or trait differences, and may underlie variability in effects of rewards on behavior. Increased reward reactivity in adolescence may contribute to known peaks in sensation seeking, which are thought to be adaptive for gaining novel experiences and specializing the neurobiological pathways required to transition to independence in adulthood. These dynamic changes in DA-related neurophysiology may underlie the emergence of psychiatric disorders in adolescence that are related to DA-ergic dysfunction including schizophrenia, mood disorders, and substance use disorders.

Code accessibility

Custom R code for all statistical analyses detailed in the paper will be made available on github prior to final publication.

CRediT authorship contribution statement

A.C.P, B. Luna, B. Larsen, F.C., and B.T.C., designed the study; A.C.P., F.C., B.T.C., B. Larsen, and W.F., analyzed the data; A.C.P., drafted the manuscript with input from F.C., B.T.C, B. Larsen, and B. Luna.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data Availability

Data will be made available on request.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.dcn.2022.101100.

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