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Delay of gratification is associated with white matter connectivity in the dorsal prefrontal cortex: a diffusion tensor imaging study in chimpanzees (*Pan troglodytes*)

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Individual variability in delay of gratification (DG) is associated with a number of important outcomes in both non-human and human primates. Using diffusion tensor imaging (DTI), this study describes the relationship between probabilistic estimates of white matter tracts projecting from the caudate to the prefrontal cortex (PFC) and DG abilities in a sample of 49 captive chimpanzees (*Pan troglodytes*). After accounting for time between collection of DTI scans and DG measurement, age and sex, higher white matter connectivity between the caudate and right dorsal PFC was found to be significantly associated with the acquisition (i.e. training phase) but not the maintenance of DG abilities. No other associations were found to be significant. The integrity of white matter connectivity between regions of the striatum and the PFC appear to be associated with inhibitory control in chimpanzees, with perturbations on this circuit potentially leading to a variety of maladaptive outcomes. Additionally, results have potential translational implications for understanding the pathophysiology of a number of psychiatric and clinical outcomes in humans.

1. Introduction

One of the main challenges in the field of neuroscience is to understand the development and evolution of the brain in relation to emergent behavioural and cognitive processes that define the human species relative to other primates. A particularly important process is the need to control emotional and behavioural impulses towards delay of gratification (DG). The ability to delay immediate gratification is critically important for a plethora of important developmental outcomes in both non-human and human primates. In non-human primates, the ability to delay immediate gratification for a more desirable, future reward is associated with a number of advantages, including access to food as well as potential mates [1,2]. Individual variation in these abilities therefore influences not only immediate outcomes but also long-term functioning, including in the areas of reproductive success, foraging efficiency and success, and even tool manufacturing and use [3,4]. Similarly, in humans, individual variability in self-control abilities, both cross-sectionally and prospectively, predict a range of social, cognitive, academic and psychopathological outcomes, including (potentially most notably) attention deficit/hyperactivity disorder (ADHD) [5,6]. Individual variability in DG abilities therefore represents important behavioural phenotypes of predictive utility offering a promising avenue through which to elucidate pathways to various behavioural outcomes. As such, explication of the underlying neurological processes that give rise to individual variability in DG will allow for a more comprehensive understanding of mechanisms associated with not

only normal variability in these abilities but potentially also the physiology of more pathological outcomes.

With regard to neuroanatomical correlates, the prefrontal cortex (PFC) and areas of the striatum (i.e. caudate) are two regions of particular interest as they appear to be brain areas that are most notably disrupted, with regard both to structure and connectivity, among non-human and human individuals with impaired DG abilities [6,7] and DG-related clinical presentations (i.e. ADHD) [8–10].

Indeed, fronto-striatal regions appear to be particularly important with regard to the ability to delay gratification, or to suppress specific kinds of behavioural processes in the presence of pre-potent stimuli that exert strong stimulus control over behaviour [11]. Although not unequivocal (for a comprehensive review, see [12]), lesion studies in both non-human animals and humans provide evidence of the importance of these brain structures, both independently and in concert, with variation in self-control abilities. Notably, non-human animals with lesions to the PFC and associated striatal regions have been described as impulsive and stimulus bound; that is, their behaviour is captured by immediate pre-potent stimuli that elicit strong reactions, and they are unable to inhibit these urges and engage in more thoughtful, planned behaviours that will result in future reward [11,13,14]. Further, in humans, there are significant developmental changes in the ability to resist the temptation for an immediate reward and wait for a larger reward in the future, which correspond to increasing maturation and connectivity in the PFC and striatum [15]. Meta-analytic findings of the structural imaging literature provide additional support for the role of the right caudate, specifically, and various prefrontral regions [16]. Prospective longitudinal data have further underscored the importance of these brain structures as DG in childhood predicts differences in rightward frontostriatal circuitries four decades later [6,7].

Taken together, the neuroscience literature clearly implicates regions of the fronto-striatum as promising neuroanatomical correlates of individual variability in DG. Nonetheless, although there appears to be some consensus in the literature concerning individual brain regions that are associated with DG and related abilities, it is likely that these regions contribute interactively [12]. Indeed, the role of various neuroanatomical structures probably depends to a considerable extent on interactions with other cortical and subcortical areas. Therefore, anatomical connectivity patterns of brain regions are likely to be as important in determining function as the regions themselves, underscoring the need for explicit examinations of these connections. Surprisingly, at present, these data are largely absent from the empirical literature, with no research to date examining the integrity of white matter connectivity between these regions in non-human primates.

Diffusion tensor imaging (DTI) is a technique for examining white matter microstructure, allowing for estimates of the integrity of pathways within neural networks [17]. Probabilistic tractography, a form of DTI analysis, delineates desired white matter tracts, providing information on white matter integrity within hypothesized regions of interest (ROIs). Specifically, by modelling diffusion properties, this technique estimates fibre orientation and reconstructs the white matter pathway on a voxel-by-voxel basis [18]. Once the connection between regions has been delineated, the resulting tract can then be examined with respect to an external variable of interest (i.e. group membership, individual variation on a behaviour/task of interest, etc.).

In this study, probabilistic tractography was employed to examine the integrity of white matter connectivity between the caudate and PFC, and was then subsequently correlated with individual variation in DG in a sample of chimpanzees. Despite the significant interest in DG abilities across different primate and non-primate species [2] and how these abilities might be linked to changes in cortical organization [19], there are no studies that have examined neurobiological or neuroanatomical correlates of individual differences in DG abilities within a species. Such studies are important because they would address the question of whether similar neuroanatomical regions or networks underlie DG abilities in human and non-human animals, a topic largely ignored, but implicit in all purely behavioural studies. In our view, studies with chimpanzees are well suited for neurobiological examinations of DG because a number of comparative studies have shown that they and other great apes exhibit significantly better delayed gratification and related skills than other non-human primates [20,21]. Further, though important differences are evident between the brains of humans and chimpanzees [22,23], there are a number of features of great ape brains that differ from more distantly related Old and New World monkeys that may underlie their superior DG performance, such as increased cortical gyrification [24], higher densities in dopaminergic and serotonergic receptors in the PFC [25,26], larger than predicted anterior insular cortex [27], higher densities of Von Economo neurons in the anterior cingulate and fronto-insular cortex [28], and a delayed maturation of synaptogenesis in the frontal cortex compared with sensorimotor regions [29]. Most of these dimensions of cortical organization have been implicated in a variety of higher-order cognitive, social and emotional processes in primates.

(a) This study

To investigate microstructure integrity of white matter, we applied probabilistic tractography to a sample of chimpanzees and examined associations with individual variation in DG abilities. Specifically, the purpose of this study was to delineate white matter tracts projecting from the caudate to the PFC. We chose to seed from the entire caudate to ensure that we captured both the ventral and dorsal striatum. These tracts were then used to quantify and examine associations with DG abilities, with regard to acquisition (i.e. training) as well as maintenance. Given the large literature on frontostriatal correlates of DG and related abilities [6,7,16], we hypothesized significant associations between reconstructed white matter tracts and DG abilities, particularly in the right hemisphere.

2. Method and materials

(a) Subjects

The sample consisted of 49 captive chimpanzees including 20 males ($M_{age} = 19.30 \pm 5.99$) and 29 females ($M_{age} = 19.54 \pm 7.15$) ranging in age from 9 to 35 years that were members of the Yerkes National Primate Research Center (YNPRC) colony of apes. Chimpanzees were housed in social groups ranging from 5 to 14 individuals. As described below, DG training and variable interval in reward delivery data was available on 43 and 39 subjects, respectively, resulting in unequal sample sizes across analyses.

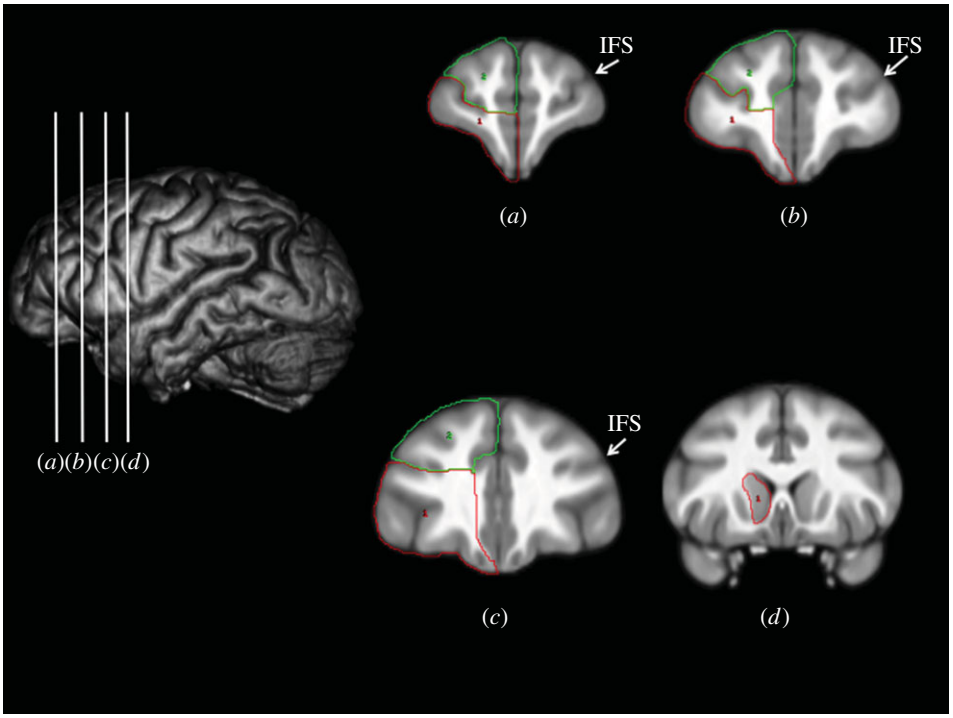

Figure 1. (*a–c*) Examples of the dPFC (green, Object 2) and oPFC (red, Object 1) traced on frontal cortex moving anteriorly to posteriorly. Note that in the more posterior sections (*b*,*c*), the anterior cingulate cortex was present and was used as the medial border rather than the mid-sagittal sulcus (see text). IFS, inferior frontal sulcus. (*d*) Example tracing of the caudate (red). (Online version in colour.)

(b) Image acquisition and procedure

All chimpanzees were scanned during their annual physical examination. Because the collection of DTI scans were tied to the chimpanzee's annual physical examination, the duration of time between scanning and the onset of behavioural testing varied across subjects. Time between collection of DTI scans and the beginning of DG testing ranged from four to 54 months (mean = 33.30 months $\pm$ 11.90). DTI scans followed standard procedures at the YNPRC and were designed to minimize stress. Thus, the animals were first sedated with ketamine (10 mg kg^{-1}) or telazol (3–5 mg kg^{-1}), and were subsequently anaesthetized with propofol (40–60 mg (kg h^{-1})). They were then transported to the scanning facility and placed in a supine position in the scanner with their head in a human-head coil. Diffusion-weighted data were acquired on a 3.0 T scanner at YNPRC (Siemens Trio). Two sets of whole brain diffusion-weighted data with a single-shot EPI sequence with a *b*-value of 1000 s mm^{-1} with 60 diffusion directions were acquired; plus one image without diffusion weighting (*b*-value of 0 s mm^{-2}). Data were acquired transaxially (FOV = 243 $\times$ 243) using 42 contiguous slices with no gap, which covers the entire brain with resolution of 1.9 $\times$ 1.9 $\times$ 1.9 mm. Averages of two sets of diffusion-weighted data were collected per subject with phase-encoding directions of opposite polarity (left–right) to correct for susceptibility distortion. Upon completion of the scan, chimpanzees were singly housed for 2–24 h to permit close monitoring and safe recovery from the anaesthesia prior to returning to their home social group.

(c) Seed masks

As seed masks for tractography analyses, we manually traced ROIs on a T1-weighted chimpanzee template brain [30]. To define ROIs, we adopted the landmarks used in previous research [30,31] in defining the orbital (oPFC) and dorsal (dPFC) PFC and the caudate in serial coronal images (figure 1). Beginning at the first image anterior to the genu of the corpus callosum and following rostrally to the frontal pole, for the oPFC, a line was drawn from the surface of the inferior frontal sulcus (IFS) sulcus to its most medial point. A second line was then drawn from the medial point of IFS to the mid-sagittal sulcus for all images anterior to the cingulate gyrus. In the images where the cingulate gyrus was visible, the medial border was the grey matter adjacent to the mid-sagittal sulcus. The dPFC was outlined by laterally tracing on the surface of the brain from the IFS to the upper, dorsal most mesial point. From there, a line was drawn that connected the most medial point of all frontal sulci between the most mesial point and the IFS sulcus. If the anterior cingulate cortex was visible, the dPFC included all grey matter superior but not inferior to the cingulate sulcus. Furthermore, the medial border for the dPFC was the lateral tip of the cingulate sulcus. Tracings of the caudate were conducted in the coronal plane and were relatively straightforward. The posterior border was the anterior commissure and tracing continued anteriorly until the caudate was no longer visible. The third ventricle served as the medial border while the internal capsule served as the lateral border.

(d) Image analysis

Consistent with previously proposed methods [18], probabilistic tractography between the caudate and PFC targets was performed using the diffusion toolbox (FDT) available in the Oxford Center for Functional Magnetic Resonance Imaging software, FSL (www.fmrib.ox.ac.uk/fsl). Initial preprocessing for images included reorientation, removal of non-brain tissue (BET), and correction for head motion and

eddy current distortion (FDT). DTIFIT was performed for fitting of diffusion tensors at each voxel to create fractional anisotropy maps. To place DTI scans in the same stereotaxic space as the structural MRI scans and associated masks for each ROI, each subject's individual DTI was registered to the T1-weighted MRI template using nonlinear transformation (FNIRT) within the registration option in the FDT module. The transformation matrix from this registration was then applied to the seed space. For each subject, probabilistic fibre tractography was computed using the software module PROBTRACKX on the BEDPOSTX output to generate an estimate of the most likely connectivity distribution between the seed and the targets [18]. We used the standard parameters with 5000 sample tracts per seed voxel, a curvature threshold of 0.2, a step length of 0.5 and a maximum number of steps of 2000. Using the caudate as the seed and the two prefrontal regions as classification targets, separately for the left and right hemispheres, PROBTRACKX quantified the connectivity values between the seed mask and target masks. For each probabilistic analysis between a seed and target ROI, as a measure of white matter integrity for each tract, we calculated the number of voxels that connect the seed and target mask. We thresholded these analyses to only calculate for those voxels which showed at least 50% (2500/5000) likelihood of connectivity. Statistical analyses on these PROBTRACKX outputs were then conducted using SPSS.

(e) Delay of gratification (training)

Delay of gratification training data were available for 43 chimpanzees. Similar to procedures employed by Beran *et al*. [1,4], a transparent PVC pipe with butcher paper blocking one end of the container was inserted halfway into the subject's cage at an angle to allow grapes to be inserted and roll to the end of the pipe, but not fall into the ape's cage. In full view of the chimpanzee, the experimenter then began placing grapes into the opposite end of the pipe at a rate of about 1 every 2–3 s until either all the grapes had been placed in the pipe or the subject took the pipe. If the subject took the pipe before all the grapes had been placed inside of it, the experimenter walked away and took the remaining grapes with them. The experimenter left for 5 min, then returned and started a new trial. If a subject waited until all the grapes had been placed in the pipe before pulling it into their enclosure, the subject received all of the grapes. The next trial was administered after the ape finished eating the grapes and returned the PVC pipe to the experimenter. In short, if a subject selected the pipe before all the grapes had been delivered, they got to eat the grapes that were in the pipe but did not get a chance to perform another trial for 5 min. The chimpanzees received 10 trials per test session, starting with five grapes per trial. Once the subject had been successful in five out of six consecutive trials or five trials in a row within a test session (i.e. waited for all grapes to be transferred), the number of grapes was increased in increments of 5 up to 20 (i.e. 5, 10, 15 and then 20). In addition to computing the total number of sessions needed for the subject to reach criterion and wait for 20 grapes, we also computed the number of training sessions needed to reach criterion when accumulating 5, 10, 15 and 20 grapes. This latter measure reflected the extent to which increasing the number of grapes might differentially influence the chimpanzee's performance.

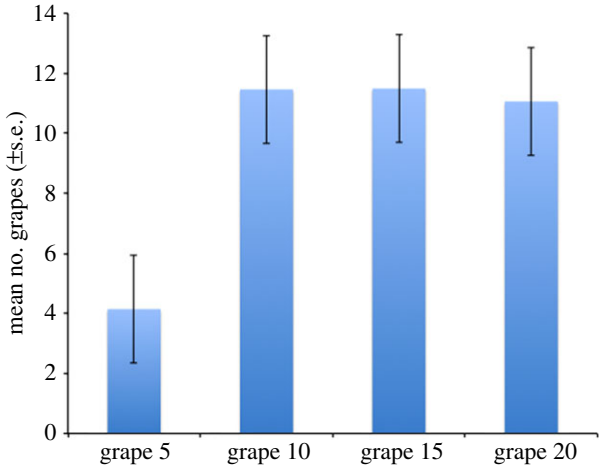

Figure 2. Mean number of test sessions (±s.e.) needed to reach criterion in waiting for 5, 10, 15 and 20 grapes. (Online version in colour.)

(f) Delay of gratification (variable interval in reward delivery)

Variable interval in reward delivery following training data was available for 39 chimpanzees. After each chimpanzee reached the 20 grape DG criteria, we tested their DG abilities when progressively increasing the interval between the delivery of each individual grape. For this assessment, the testing procedure was identical to the training procedure with one small variation. During the delivery of the grapes by the experimenter, the interval increased by 1 s upon successive presentations. Thus, after the delivery of grape 1, there was a 1 s interval before the next grape was delivered. This was repeated for each successive grape up to the maximum, in which 20 s transpired between the delivery of the 19th and 20th grape in the test session. Each chimpanzee received three test sessions, with five trials within each test session. Each trial within a test session was separated by 2 min. The dependent measure was the number of grapes accumulated within each trial and session.

3. Results

(a) Behavioural data

(i) Training

In the initial analysis, we compared DG acquisition rates in males and females when increasing the criterion from 5 to 20 grapes using a mixed-model analysis of variance. The number of training sessions needed at each criterion level (5, 10, 15 and 20 grapes) was the repeated measure, while sex was the between-group factor. We found a significant main effect for training criterion $F_{3,141} = 16.318$, $p < 0.001$ (figure 2). Pairwise comparison *post hoc* tests revealed that the number of trials needed to reach criterion was significantly higher for 10 (mean = 11.458, s.e. = 1.07), 15 (mean = 11.49, s.e. = 1.36) and 20 (mean = 11.059, s.e. = 1.44) grapes compared with 5 (mean = 4.15, s.e. = 0.72). No other significant differences were found.

(ii) Delayed interval

We next performed a mixed-model analysis with session ($n = 3$) and trial ($n = 5$) serving as repeated measures,

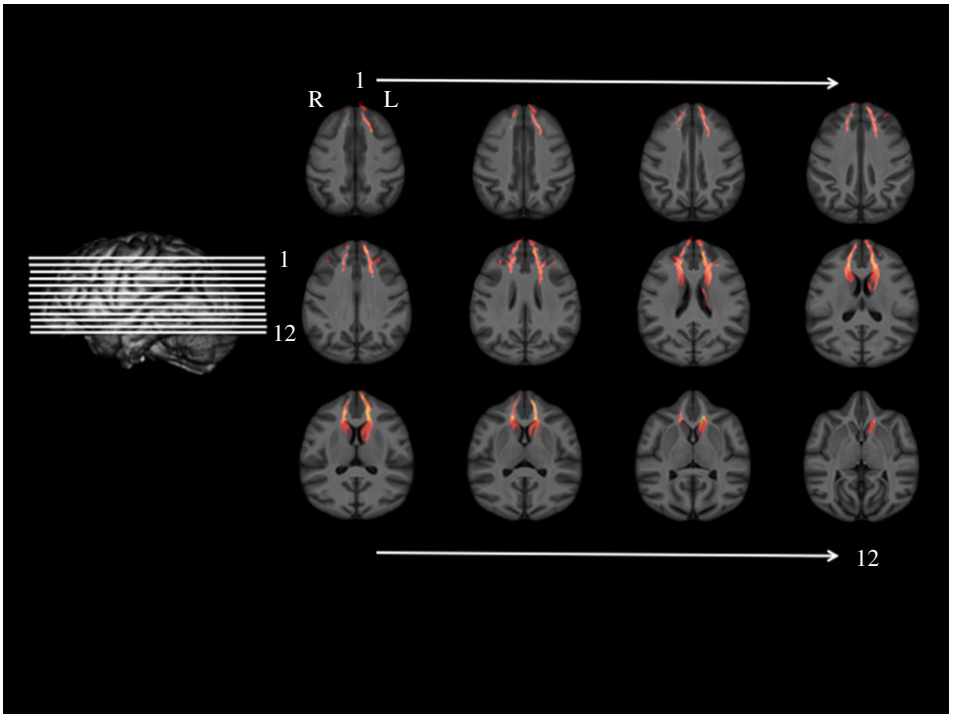

Figure 3. Series of 12 serial axial views (1 = most dorsal, 12 = most ventral) of the dPFC tract projected onto the T1-weighted template brain. Note that the left hemisphere tract is larger, and this was a statistically significant difference (see Results). (Online version in colour.)

while sex was the between-group factor. A significant main effect for session was found ($F_{2,184} = 9.058$, $p < 0.001$). *Post hoc* analysis showed that the chimpanzees accumulated fewer grapes during session 1 (mean = 9.64, s.e. = 0.542) compared with sessions 2 (mean = 11.24, s.e. = .594) and 3 (mean = 11.26, s.e. = 0.558). No other significant main effects or interactions were found.

(b) Tractography

We first examined structural connections between the caudate seed and the PFC ROI targets. Specifically, we examined the number of voxels projected from the caudate and reaching each target of interest, thresholded at 50% likelihood of connectivity, separately for the right and left hemispheres (figure 3). Results of paired-sample *t*-tests indicated that the number of reconstructed fibres was significantly higher in the tract from the caudate to the oPFC than the tract to the dPFC in both the right ($t_{48} = -9.89$, $p < 0.001$) and left ($t_{48} = -5.88$, $p < 0.0001$) hemispheres. Further, although there were no differences in reconstructed fibres between the two hemispheres with regard to caudate to oPFC projections ($t_{48} = 0.74$, $p > 0.70$), there were significantly more voxels in the caudate to dPFC tract in the left compared with right hemisphere ($t_{48} = -2.33$, $p < 0.03$). Thus, there was a leftward asymmetry in the dPFC tract.

(i) Preliminary age and sex effects analyses

Before assessing the association between the number of voxels between the caudate and each PFC target with regard to variability in DG, we performed a series of initial analyses to test for sex differences and potential associations with age. For these analyses, we performed a multivariate analysis of covariance analysis with sex as the between-group factor and age as the covariate. The number of voxels projected from the caudate to each of the two PFC regions in each hemisphere of the brain were the dependent variables. Sex was not found to have a significant effect on the number of voxels projected from the caudate to either the oPFC or the dPFC bilaterally (all $F < 3.35$, all $p > 0.07$). Age, however, was found to be significantly positively associated with the number of voxels in the caudate to the left ($F_{1,48} = 8.36$, $p < 0.01$) and right ($F_{1,48} = 4.15$, $p < 0.05$) oPFC tracts. Age was not significantly associated with the number of voxels in the caudate to dPFC tract in either hemisphere. Further, with regard to age or sex effects on DG, neither age (all $p > 0.10$) nor sex (all $p > 0.08$) were associated with DG abilities on either the training phase or any of the three test trials.

(ii) Association between tractography and delay of gratification

To investigate the association between the number of reconstructed fibres within each tract projecting from the caudate and DG abilities, a series of linear regression models investigating the association between the number of thresholded voxels within each tract and DG performance during the training phase and each of the three interval test trial phases were run. Given variability in age, sex and time between collection of DTI scans and DG testing, age, sex and time between scan collection and behavioural testing were included as a covariates in all models. As shown in table 1, DG abilities during the training phase, as indicated by the number of training sessions needed to reach criterion at each level, were significantly and negatively associated with the number of voxels projected from the caudate to the dPFC in the right hemisphere (median $\beta = -0.449$ across four training sessions), associations that survived false discovery rate (FDR) corrections for multiple comparisons ($q = 0.05$). These associations did not emerge with regard to projections from the caudate to the dPFC in the left hemisphere; neither right nor left hemisphere tracts from the caudate to the oPFC were associated with DG during the training phase. Lastly, none of the reconstructed tracts were associated with DG performance during the interval testing phases.

Table 1. Associations between reconstructed fibres projected from the caudate to the PFC and DG controlling for age, sex and time between DTI scan and DG data collection. $n = 43$ for DG training and $n = 39$ for DG interval testing, as described in text. Correlations shown in bold survived false discovery rate (FDR) correction for multiple comparisons ($q = 0.05$). DG, delay of gratification; PFC, prefrontal cortex.

	DG training					DG interval testing		
	5	10	15	20	total	test 1	test 2	test 3
	β	β	β	β	β	β	β	β
right dorsal PFC	**−0.466****	**−0.534****	**−0.431****	**−0.400***	**−0.411***	0.011	0.163	0.223
right orbital PFC	−0.280	−0.293	−0.121	−0.076	−0.095	−0.229	−0.018	−0.141
left dorsal PFC	−0.165	−0.175	−0.222	−0.185	−0.175	−0.171	−0.038	−0.086
left orbital PFC	−0.005	−0.089	0.018	−0.025	−0.057	−0.094	−0.023	−0.042

*$p < 0.05$; **$p < 0.01$.

4. Discussion

This study represents the first investigation of the association between probabilistic estimates of white matter tracts projecting from the caudate to the PFC and DG abilities in chimpanzees to date. Consistent with the hypotheses, the integrity of white matter connectivity between striatal and PFC regions appears critical for DG. Specifically, this association consistently emerged during the training (i.e. acquisition phase) but not during the interval testing (i.e. maintenance/generalizability phase).

Preliminary analyses of the behavioural data during the training phase showed that increasing the number of grapes to reach criterion from 5 to 10 significantly affected DG performance. After 10 grapes, however, increases in the number of grapes needed to reach criterion (i.e. 15, 20) did not significantly influence performance. Neither age nor sex was associated with DG abilities. Further, before investigating associations between connectivity patterns and DG abilities, consistent with a large existing literature (e.g. [15]), we confirmed our hypotheses that the caudate, dPFC and oPFC are connected via direct structural white matter tracts with this projection stronger to the oPFC than to the dPFC bilaterally. Additionally, whereas sex was not associated with the integrity of any of the reconstructed tracts, age was significantly and positively associated with connectivity from the caudate to the oPFC bilaterally. Lastly, overall, we found a significant leftward asymmetry in the caudate–dPFC tract. Though population-level neuroanatomical asymmetries have historically been considered uniquely human [32,33], our findings support an increasing body of evidence of asymmetries in non-human primates, notably chimpanzees, in terms of volumetric and white matter connectivity [34–36].

With regard to associations between the integrity of frontostriatal connectivity and DG abilities, after statistically controlling for age, sex and time between DTI scan and DG data collection, we found greater white matter connectivity between the right caudate and right dPFC to be significantly associated with the acquisition (i.e. training phase) but not the maintenance (i.e. interval testing) of DG abilities. This finding survived an FDR correction for multiple comparisons and was evident across all training criterion levels (i.e. 5, 10, 15 and 20 grapes). These results suggest that individual variability in the learning of DG abilities is clearly correlated with frontostriatal connectivity, with increased integrity of tracts associated with more rapid DG learning. Once individuals reached criterion, however, these abilities were no longer associated with white matter integrity in these tracts. These results have a number of potential explanations. For example, it may be that acquisition and maintenance of DG are subserved by different functional connections. Another potentially more parsimonious explanation may be that once subjects are able to reach criterion, the variability in performance decreases as a result of decreased task difficulty, resulting in attenuated associations. In short, with training, we may have reached the chimpanzees' asymptotic DG performance, and thus we were only seeing the ceiling effects in the interval test.

A critical aspect of this research is its translational value to human development and pathophysiology of clinical outcomes. Indeed, it is important to note that this study links to Mischel's [37–40] seminal research on self-control abilities, as assessed by a parallel DG task to the one used in this study. Specifically, in humans, Mischel and co-workers have found DG abilities at age 4 years to predict planning and reasoning abilities, control in the context of negative emotions, coping and even standardized testing scores at 16–18 years of age [38,39], and higher educational attainment, better coping with stress, lower interpersonal difficulties and substance use, and even higher self-esteem and self-worth more than 20 years later [40]. Whereas a number of tasks have been used in the literature to assess self-control abilities, a number of limitations exist. Accumulation tasks, such as the DG task used in this study, as well as the original Mischel task, in which subjects must, in the presence of differing quantities of food, wait for all items to be delivered before taking them, however, have been found to overcome many of these limitations [1,4]. Specifically, in many self-control tasks, it is impossible to determine whether the subject is actually selecting the reward that requires increased delayed gratification or is simply selecting the food with the greater quantity. It is generally accepted that when given a choice, many animals, including both humans and chimpanzees, will choose the larger over a smaller quantity of the same food. Further underscoring the strength of the accumulation task is a large comparative literature suggesting that while primates can all perform many of the other self-control tasks, chimpanzees and humans, but not monkeys, are uniquely able to wait for food [1]. Underscoring the translational value of this study, therefore, the DG task used in this study, and the acquisition phase of this task specifically,

are closely linked to the original Mischel task [37], in that they explicitly require that the subjects delay their gratification.

(a) Limitations

There are several limitations to this study. First, consistent with the question of causality raised above, the cross-sectional correlational nature of the design does not allow for causal inferences to be made. Second, we used landmarks to define the PFC and caudate that have been previously used in comparative studies between humans and apes, but it must be recognized that the morphological landmarks are not entirely the same in humans and apes [31,41,42]. Furthermore, the relationship between sulcal landmarks and cytoarchitectonic boundaries defining specific cortical regions are not particularly strong in either humans or apes [43]. Thus, we avoided using specific Brodmann area designations to describe our morphological ROIs, resulting in the need for further investigation in both humans and apes. On a related note, the primary landmark used to distinguish dorsal and orbital PFC was the IFS, which has been reported to be highly variable across individual chimpanzees [44]. Additionally, there are multiple structures that can be considered as part of the striatum, and we chose to focus on one (the caudate). Further, as there are no cytoarchictectural landmarks available to distinguish among various regions of the caudate, we seeded from the entire structure. Nonetheless, based on the probabilistic approach used, we were able to determine that the most consistent connections between dPFC and the caudate were largely restricted to the dorsal and lateral portion of the caudate (see the figure in the electronic supplementary material). The fact that we used a template brain on which to draw the ROIs and all subjects were registered to that template made addressing the issue of variability easier, but this comes with some limitations. Notably, this commonly used approach assumes that when ROIs are drawn on the template brain and projected back onto individual brains in native space, the landmarks remain stable and consistent across subjects. This may not be the case for every individual.

It is important to note that, despite the obvious advantages of probabilistic tractography, these analyses provide neither information concerning the direction of the reconstructed white matter fibre pathways nor whether they are direct measures of white matter tracts. Instead, they are mathematical estimations of streamlines between the chosen brain regions [45]. Lastly, one important yet unresolved issue has to do with whether frontostriatal connectivity integrity associated with DG has a causal association with associated behavioural symptoms (i.e. inattention, impulsivity, hypersensitivity to reward) [6]. Although both developmental [46,47] and pharmacological [48] studies strongly suggest a causal association, it will be imperative for future research to examine the effects of targeted interventions, with regard to generalization of DG and related abilities, as well as functional connectivity changes.

Limitations notwithstanding, the results of this study implicate frontostriatal white matter connectivity in the explanation of individual variability in DG abilities in chimpanzees. As noted earlier, chimpanzees represent a particularly well-suited model species for such investigations. Given the clear translational value of this research to humans, results have implications for understanding the pathophysiology of a variety of behavioural outcomes in humans, including (but not limited to) ADHD. Indeed, perturbations on this circuit probably have transdiagnostic implications for a variety of behavioural problems characterized by weak inhibitory control and DG [5,6].

Ethics. All procedures were approved by the Institutional Animal Care and Use Committees at YNPRC. All procedures adhered to the National Institutes of Health and Institute of Medicine guidelines for the ethical treatment and use of chimpanzees in research.

Data accessibility. The dataset supporting this article is available at Dryad Digital Repository: http://dx.doi.org/10.5061/dryad.b20t3.

Authors' contributions. R.D.L. participated in the conception and design of the study, carried out the statistical analyses and drafted the manuscript; J.P.T. participated in data collection, performed all the preprocessing of the DTI scans and provided critical revisions to the manuscript; W.D.H. participated in the conception and design of the study, participated in data collection and provided critical revisions to the manuscript. All authors gave final approval for publication.

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