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Delay Discounting and Frontostriatal Fiber Tracts: A Combined DTI and MTR Study on Impulsive Choices in Healthy Young Adults

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Delay discounting, a measure of impulsive choice, has been associated with decreased control of the prefrontal cortex over striatum responses. The anatomical connectivity between both brain regions in delaying gratification remains unknown. Here, we investigate whether the quality of frontostriatal (FS) white matter tracts can predict individual differences in delay-discounting behavior. We use tract-based diffusion tensor imaging and magnetization transfer imaging to measure the microstructural properties of FS fiber tracts in 40 healthy young adults (from 18 to 25 years). We additionally explored whether internal sex hormone levels affect the integrity of FS tracts, based on the hypothesis that sex hormones modulate axonal density within prefrontal dopaminergic circuits. We calculated fractional anisotropy (FA), mean diffusivity (MD), longitudinal diffusivity, radial diffusivity (RD), and magnetization transfer ratio (MTR), a putative measure of myelination, for the FS tract. Results showed that lower integrity within the FS tract (higher MD and RD and lower FA), predicts faster discounting in both sexes. MTR was unrelated to delay-discounting performance. In addition, testosterone levels in males were associated with a lower integrity (higher RD) within the FS tract. Our study provides support for the hypothesis that enhanced structural integrity of white matter fiber bundles between prefrontal and striatal brain areas is associated with better impulse control.

Keywords: delay discounting, DTI, frontostriatal tracts, impulsivity, testosterone

Introduction

Impulsive choice in the context of delay discounting involves an increased preference for immediate rewards over more long-term advantageous, but delayed, outcomes (Ainslie 1975). This form of impulsivity, regulated by dopamine neurotransmission (van Gaalen et al. 2006), is adaptive in certain situations (grabbing a "once-in-a-lifetime opportunity"), but is maladaptive in cases such as quick financial investments or impulsive shopping. This might lead, in extreme cases, to severe interference with daily functioning (Moeller et al. 2001). The current study set out to examine neural mechanisms leading to variation in this trait to ultimately be able to predict pathological forms of delay discounting, such as observed in addiction, pathological gambling (Reynolds 2006), and attention deficit/hyperactivity disorder (ADHD; Scheres, Tontsch, et al. 2010).

One set of studies using functional neuroimaging has shown that the striatum is hyper-responsive when individuals choose immediate rewards over delayed rewards (McClure et al. 2004), and the magnitude of striatal activation predicts steepness of discounting within a behavioral assessment outside the magnetic resonance imaging (MRI) scanner (Hariri et al. 2006). A second set of studies has proposed that the greater prefrontal cortex (PFC) involvement (over striatal regions) reflects enhanced top-down cognitive control and, as a result, less impulsive decision-making (Peters and Büchel 2011). Initial evidence for this presumed relation comes from studies showing that activity within lateral cortical areas shows (negative) sensitivity to the delay of rewards (Ballard and Knutson 2009). Furthermore, disrupting the (lateral) PFC, using transcranial magnetic stimulation, directly affected the preference for smaller immediate rewards over larger delayed rewards (Figner et al. 2010).

Despite the suggested relation between striatum and PFC, no study to date has examined whether enhanced anatomical connectivity between both brain regions is also related to higher delay of gratification. The presumed control over the striatum by the PFC associated with less delay aversion might reflect improved structural integrity of white matter fiber bundles that enable communication between the PFC and striatal brain regions. Recently, deficits in impulse control have been related to increased dopamine release within the striatum, partly mediated by decreased dopamine receptor binding in ascending dopaminergic projection pathways (Buckholtz et al. 2010). Moreover, altered dopaminergic signaling (excessive or diminished) has been associated with deficits in white matter integrity, especially in frontostriatal (FS) tracts (Liston et al. 2011).

The primary aim of this study was to investigate whether the quality of FS white matter tracts can predict individual differences in delay-discounting behavior. To test this hypothesis, we used a combination of diffusion tensor imaging (DTI) and magnetization transfer imaging (MTI) to assess the quality of these white matter tracts, as these complementary MRI techniques measure different microstructural properties of the brain tissue.

There is accumulating evidence that sex steroids may influence the anatomy of dopaminergic pathways (for review see Kuhn et al. 2011). For example, estradiol increases the density of terminal branching of dopaminergic neurons in the dorsal striatum and the frontal cortex of primates (Kritzer and Kohama 1998; Kritzer et al. 2003). In rats, blocking testosterone production augmented prefrontal processing, by increasing axon density of dopaminergic pathways (Aubele and Kritzer 2011). Moreover, enhanced testosterone levels

in human adults decrease functional cortico-subcortical connectivity, whereas estradiol increases functional cortico-subcortical connectivity (Peper et al. 2011).

Studies providing indirect evidence that sex hormones might modulate impulsive behavior indicate that males more often suffer from psychopathological conditions characterized by high impulsivity such as ADHD (Strüber et al. 2008) and addiction (Lenz et al. 2012). However, studies examining the direct association between sex steroids levels and impulsive behavior are limited. In females, higher testosterone levels predict lower impulse control (Bjork et al. 2001). In males, higher endogenous testosterone predicts steeper delay-discounting behavior in low impulsive subjects, whereas testosterone reduces delay discounting in high impulsive subjects (Takahashi et al. 2006).

As a secondary aim of our study, we therefore explored whether internally fluctuating sex hormones contribute to individual differences in FS microstructure, as a possible mechanism predisposing to impulsive tendencies. We hypothesize that lower integrity within FS white matter relates to increased impulsive choices. Moreover, we expect that higher testosterone levels are associated with lower FS white matter integrity, whereas higher estradiol levels are related to higher FS white matter integrity.

Materials and Methods

Participants

A total number of 40 adult subjects were enrolled in the study (20 males) between 18 and 25 years of age (mean 21.3, standard deviation [SD] 2.0). Subjects were recruited from the University of Leiden and surrounding community and had normal intelligence (mean 112, SD 8.9; approximated using 2 subtests of the Wechsler adult intelligence scale IV (WAIS-IV): Block design and similarities; Table 1). Participants were free from any history of psychiatric, endocrinological, or neurological illnesses, screened by an a priori interview.

The internal review board from the Leiden University Medical Center approved the study. All subjects gave informed consent and were paid for participation.

Impulsivity Measures

Delay-Discounting Task

A computerized version of a hypothetical delay-discounting task was used based on the paradigm described by Richards et al. (1999). In short, subjects were asked to make a series of choices, between either a small, immediately available amount of money and €10 delayed for either 2 days, 30 days, 180 days, or 365 days. For example: "What do you prefer: 1) €2 right away or 2) €10 in 30 days?" After the choice for the immediately available money, this amount was decreased on a next trial, whereas if the delayed money was preferred, the amount of immediately available money on the next trial was increased (decreasing adjustment algorithm; Du et al. 2002). Trials with different delays were presented in a mixed fashion.

So-called "indifference points" for each delay were calculated: That is, the amount of immediately available money the participant considered to be equivalent to the €10 delayed reward was taken to indicate the subjective value of the delayed rewards. Based on these indifference points, the area under the discounting curve (AUC) was obtained, an often-used measure of amount of discounting (Myerson et al. 2001; Paloyelis et al. 2010). The normalized AUC ranges from 0 (complete discounting) to 1 (no discounting), implying negative scoring: The smaller the AUC, the faster people discount the delayed reward and the more impulsive (or delay aversive) they are.

Although participants were not directly paid for the discounting task, choices on a hypothetical delay-discounting task substantially and significantly correlate (r's up to 0.74) with choices on a delay-discounting task with real rewards (Bickel et al. 2009; Scheres, Sumiya, et al. 2010). Furthermore, the discounting curves of real and hypothetical tasks are comparable (Madden et al. 2003, 2004).

Self-Reported Impulsivity

To obtain a secondary measure of impulsive traits, the Barratt Impulsiveness Scale (BIS-11) was administered (Patton et al. 1995). The BIS-11 questionnaire comprises of subscales of motor impulsivity ("I act without thinking"), non-planning impulsivity ("I am not interested in the future, but in today"), and attentional impulsivity ("I have difficulties sitting still during lectures"). Furthermore, monthly alcohol use and smoking were measured using a self-report questionnaire (Scholte et al. 2001).

Hormonal Sampling and Analyses

Testosterone and estradiol were determined in morning saliva (collected immediately after waking up) of both male and female participants. Salivary testosterone was measured by isotope dilution–online solid-phase extraction liquid chromatography–tandem mass spectrometry (ID–XLC–MS/MS) as described earlier (Bui et al. unpublished data; de Ronde et al. 2011). Intra-assay coefficient of variation (CV) was 11%, 4%, and 2% at 10, 140, and 900 pmoL/L, respectively and inter-assay CV was 5% at 200 and 2000 pmol/L, respectively.

Salivary estradiol was measured using an enzyme linked immuno sorbant assay (DRG Instruments, Marburg, Germany). Intra-assay CV was 11% and 6% at 2.7 and 7.1 pg/mL, respectively.

Male data showed one extreme outlier (>3 SD) in the data of 1 male. Excluding this outlier in the analyses did not change the results. We chose to report the data without the outlier in those analyses that included hormones as predictor, leaving the male (hormonal) sample at 19 participants.

Both females using oral contraceptives ($N = 16$) as well as not using contraceptives ($N = 4$) were included in the study. Females using contraceptives collected saliva on the last day within their stopping period (day 7). Similarly, to control for hormonal fluctuations across the menstrual cycle, females collected saliva on the same day within the early follicular phase of the menstrual cycle (day 7), when hormone levels are relatively low (Mihm et al. 2011). Females using contraceptives without a stopping period, such as hormonal intrauterine devices (e.g. Mirena), were not included in the study. As basal testosterone levels in females using oral contraceptives are lower than in non-using females (Liening et al. 2010), analyses were repeated excluding the 4 females not using contraceptives.

Imaging Acquisition

Scans were acquired on a 3-Tesla Philips Achieva MRI system (Best, The Netherlands). Two transverse DTI scans were acquired with the following parameter settings: 30 diffusion-weighted volumes with

Table 1
Demographic characteristics of the sample (means [SD])

	Males ($N = 20$)	Females ($N = 20$)
Age (years)	21.9 (2.0)	21.0 (1.9)
Estimated IQ	112.4 (8.2)	112.3 (10.2)
Delay-discounting AUC	0.52 (0.16)	0.65 (0.22)*
FS FA	0.37 (0.009)	0.36 (0.013)**
FS MD (mm^2/s)	0.00079 (0.00001)	0.00079 (0.00002)
Testosterone (pmol/L)	450.3 (200.6) ($N = 19$)	24.6 (8.6)***
Estradiol (pg/mL)	3.4 (1.7) ($N = 19$)	3.0 (1.6)
White matter volume (mL)	537.6 (59.8)	485.6 (47.7)***

Note: AUC, area under the discounting curve (normalized); FA, fractional anisotropy; FS, frontostriatal; IQ, intelligence quotient; MD, mean diffusivity. Estimated IQ is based on WAIS-IV subscales similarities and block design.
*$P < 0.05$.
**$P < 0.001$.
***$P < 0.0001$.

different non-collinear diffusion directions (Jones et al. 1999) with *b*-factor 1000 s/mm^2 and 5 diffusion-unweighted volumes (*b*-factor 0 s/mm^2); parallel imaging sensitivity encoding for fast MRI (SENSE) factor = 3; flip angle 90°; 75 slices of 2 mm; no slice gap; reconstruction matrix 128 × 128; field of view (FOV) = 240 × 240 mm; echo time (TE) = 69 ms; repetition time (TR) = 7315 ms; no cardiac gating; and scan duration = 271 s (542 s in total). The second DTI set had identical parameter settings as used for the first DTI set except that it was acquired with a reversed *k*-space readout direction enabling the removal of susceptibility artifacts during post-processing (Andersson et al. 2003).

The transverse magnetization transfer scan consists of 2 volumes (TR = 65.795 ms; TE = 2.2 ms; FOV = 240 × 190 × 180; reconstructed voxel size 1.875 × 1.875 × 2 mm^3; 95 overcontinuous slices; slice thickness 4 mm; slice gap −2 mm; flip angle 18°, parallel imaging SENSE factor (right-left) = 2) with an additional off-resonance prepulse (frequency offset 1100 Hz, 620°, 3-lobe sync-shaped) applied for the second volume, yielding a total scan duration of 176 s.

A high-resolution 3D T_1-fast field echo scan for anatomical reference was obtained (TR = 9.760 ms; TE = 4.59 ms, flip angle = 8°, 140 slices, 0.875 × 0.875 × 1.2 mm^3 voxels, FOV = 224 × 168 × 177 mm^3) with a total scan duration of 296 s. All T1 scans were reviewed and cleared by a radiologist. No anomalous findings were reported.

Image Processing

To correct for susceptibility artifacts, the 2 DTI scans were combined into 1 DTI scan using the software developed by Andersson et al. (2003). In a second step, we realigned the DTI set which simultaneously corrects for gradient-induced distortions and head movement (Andersson and Skare 2002). Next, for each voxel in the DTI scan, the diffusion tensor was computed using M-estimators to reduce the influence of possible outliers (Chang et al. 2005). After diagonalization of the diffusion tensor, the major eigenvector of the tensor was computed, that is, the eigenvector with the largest eigenvalue (λ_1), which is assumed to point in the direction parallel to the underlying fiber bundle as water diffuses much more easily in the direction parallel to the axons than in the perpendicular direction. This largest eigenvalue λ_1 is also known as the longitudinal diffusivity (LD; $D_\parallel$), while the average of the eigenvalues corresponding to the 2 minor eigenvectors (i.e. $[\lambda_2 + \lambda_3]/2$) is known as the radial diffusivity (RD; $D_\perp$). Two other measures derived from the diffusion tensor were computed: The mean diffusivity (MD), which is defined as the average eigenvalue (i.e. $[\lambda_1 + \lambda_2 + \lambda_3]/3$) and the fractional anisotropy (FA; Basser and Pierpaoli 1996) defined by:

$$\mathrm{FA} = \sqrt{\frac{3}{2}\left(\frac{(\lambda_1 - \bar{\lambda})^2 + (\lambda_2 - \bar{\lambda})^2 + (\lambda_3 - \bar{\lambda})^2}{\lambda_1^2 + \lambda_2^2 + \lambda_3^2}\right)}$$

where,

$$\bar{\lambda} = \frac{\lambda_1 + \lambda_2 + \lambda_3}{3}.$$

The FA provides information on the shape of the diffusion profile of water molecules and ranges between 0 (no preferred diffusion direction) and 1 (highly preferred diffusion direction). Compared with FA values found in gray matter (typically near zero), FA values found in white matter are relatively high, since the diffusion profile of water in white matter is highly anisotropic. For this reason, FA is often considered a measure of directionality (or "integrity") of the white matter fiber bundles.

Magnetization transfer ratio (MTR), a putative measure of macromolecule concentration (including myelin), was computed using both the MTI volume with the magnetization prepulse (I_m) and the image without the magnetization prepulse (I_0), according to: $(I_0 - I_m)/I_0$. A high MTR value represents much signal loss, due to the presence of magnetization transfer (and a supposedly high level of macromolecules), whereas a low MTR value represents almost no signal loss, due to the absence of magnetization transfer. We note however that, due to the relative short repetition time, the MTI acquisition as used in this study is not only sensitive to changes in macromolecule concentrations but is also sensitive to changes in the amount of free bulk water (Henkelman et al. 2001; Mandl et al. 2010).

Frontostriatal Fiber Tract Selection and Creation of Volume of Interest

FS fiber tracts are currently not defined by tractography-based white matter atlases. Therefore, according to the method described by de Zeeuw et al. (2011), we constructed a study specific volume of interest (VOI) to measure FS white matter tracts. This method requires that the fiber tracts that are reconstructed for each subject in native space, are put into model space in order to create the VOI. To that end, a series of transformations were computed using the ANIMAL software package (Collins et al. 1995). First, a non-linear transformation was computed that warps the T_1-weighted scan to the colin27 model brain (Holmes et al. 1998), using cross-correlation as similarity metric. Subsequently, a rigid transformation was computed that spatially aligns the diffusion-unweighted volume of the processed DTI set with the T_1-weighted scan, using mutual information as a similarity metric.

Then, a rigid transformation was computed registering the first volume of the MTI scan with the diffusion-unweighted volume of the processed DTI set, using mutual information as a similarity metric. The transformation that warps DTI data into model space was formed by the concatenation of the "DTI-to-anatomy" and "anatomy-to-model" transformations. MTI information was warped to model space using a concatenation of the "MTI-to-DTI", "DTI-to-anatomy", and "anatomy-to-model" transformations.

Next, for each subject, the deterministic fiber assignment by continuous tracking algorithm (Mori et al. 1999) was applied to the DTI data, to reconstruct a complete set of fiber tracts in native space. We placed 8 seedpoints evenly spaced, forming a regular grid in every brain voxel. This increases the probability of finding correct fibers, as the choice of the position of seedpoints within the voxel influences the result. Fiber tract reconstruction terminated if the FA was <0.2, or if the angle of the tract exceeded 60°.

Finally, the reconstructed tracts of each individual subject were then warped to model space, using the "DTI-to-model" transformation.

In order to be included as FS white matter, tracts were required to run through both the striatum and PFC. Inclusion regions-of-interest (ROIs) were based on the automatic anatomical labeling (AAL) template (Tzourio-Mazoyer et al. 2002), including the caudate, putamen, and pallidum (AAL regions 71–76), as well as the dorsolateral, ventrolateral, and ventromedial prefrontal cortices (AAL regions 5–10; 13–16; 25–28; de Zeeuw et al. 2011). The ROIs were dilated with 2 voxels in all directions to ensure that they penetrate the white matter. Exclusion ROIs were the genu of the corpus callosum (manually delineated on the midsagittal slice), the uncinate fasciculus, and the longitudinal fascicules (manually delineated by a plane through the temporal lobes where the amygdala was located). We note that for fiber selection, all ROIs had to be defined only once, on the model brain. For an individual example of FS fiber tracts, see Figure 1*A*. All voxels within the selected FS tracts were flagged, resulting in individual binary maps of FS tracts (in the model space) for each participant in the sample.

Subsequently, a "VOI" was created for FS tracts of the whole sample (de Zeeuw et al. 2011): Every voxel within the FS tract should have a fiber running through in at least 75% of the sample (i.e. thresholded at 25%; Fig. 1*B*). Then this particular voxel was flagged and added to the VOI. Within the VOI of the FS tract, DTI metrics (FA, MD, LD, and RD) and MTR were calculated for each individual subject. Moreover, whole-brain DTI parameters were also calculated.

To check for general white matter volume effects on delay-discounting behavior, total cortical white matter volume was calculated using the AAL (Tzourio-Mazoyer et al. 2002) within the FreeSurfer software package.

Statistical Analyses

To address our primary research question, Pearson's correlations were calculated between delay discounting (area under the curve

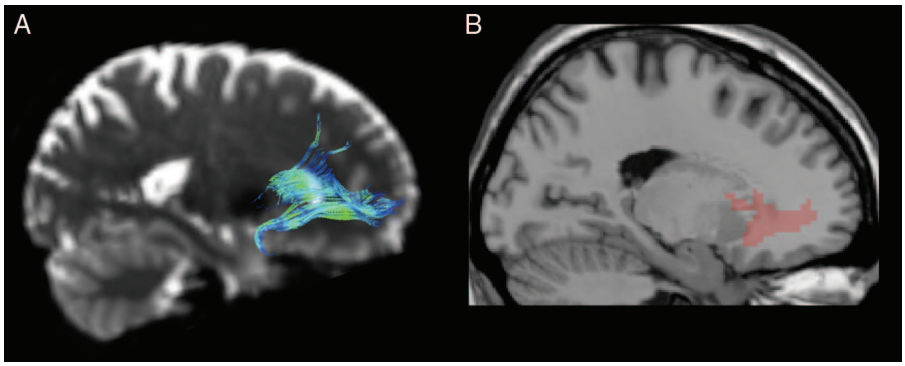

Figure 1. FS tracts of 1 individual (*A*) and binary group average VOI (*B*). The FS white matter tract within an individual subject, after applying inclusion and exclusion ROIs in model space (*A*). A VOI was created across the whole sample, where a voxel was flagged when that particular voxel had a FS fiber running through in at least 75% of the sample (*B*).

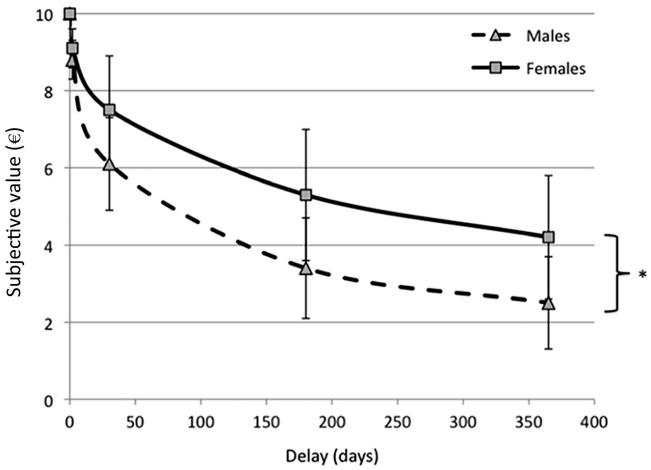

Figure 2. Delay-discounting curves of males and females ($N = 40$). In the *Y*-axis, the subjective value of €10 (with SD) is plotted against various delays (no delay, 2 days, 30 days, 180 days, and 365 days) in the *X*-axis. The AUC is significantly smaller in males than in females ($P < 0.04$).

[AUC] as well as the separate indifference points), DTI (FA, MD, LD, and RD), and MTR measures of the FS tracts. The possible contribution of age, sex, and intelligence to the delay-discounting behavior (Olson et al. 2009) and white matter volume (Lebel and Beaulieu 2011) was explored and, if significantly contributing, added as variables of no interest. Since associations between impulsivity and white matter microstructure may be modulated by secondary variables including substance abuse, we included monthly alcohol consumption and smoking as additional covariates in the analyses. As we investigated 5 white matter characteristics (FA, MD, LD, RD, and MTR), we report for these analyses whether the effect remained significant at a Bonferroni-corrected *P*-value of 0.01 (0.05/5).

To address our second research question, correlations between sex steroid levels, FS white matter measures, and delay-discounting performance were computed using non-parametric Spearman's correlations. Due to the sex-specific nature of sex steroid hormones, these correlations were computed within each sex separately.

Results

Demographic Factors

Exploring the contribution of possible confounding factors sex, age, and intelligence to delay-discounting performance and white matter indices, we found that males discounted steeper than females (i.e. make more impulsive choices; $F_{1,39} = 4.57$; $P = 0.04$; Fig. 2), and males had higher FA within the FS tract ($F_{1,39} = 11.10$; $P = 0.001$). Moreover, MD decreased with age ($r = -0.38$; $P = 0.02$).

Substance use and estimated IQ were not associated with delay-discounting performance or white matter integrity within the FS tract (*P*'s > 0.25). Total brain FA, MD, and white matter volumes were also unrelated to the delay-discounting performance (*P's* > 0.66). With respect to self-reported impulsivity, higher motor impulsivity was associated with steeper discounting ($r = 0.33$, $P = 0.04$).

Frontostriatal White Matter and Delay Discounting

With sex and age added as covariates, the analyses showed that a smaller AUC on the delay-discounting task (making more impulsive choices) was correlated with higher MD in the FS tract ($r = -0.50$, $P = 0.001$; Fig. 3). That is, more overall diffusivity in the FS tract predicts more impulsive choices. To further explore the direction of diffusion, we found that RD (diffusivity perpendicular to the length of the axons) significantly contributed to explaining individual differences in delay-discounting performance ($r = -0.52$, $P = 0.001$). Moreover, a smaller AUC was associated with lower FA in the FS tract ($r = 0.38$, $P = 0.03$), although this association did not survive a Bonferroni correction for multiple comparisons. When separate indifference points were examined, it appeared that FA, MD, and RD mainly predicted extent of discounting at the 2 longest delays, that is, 180 and 365 days (with explained variance up to 24%). The associations between DTI measures and delay-discounting performance remained significant after correcting for the substance use (MD: $r = -0.45$, $P = 0.01$; RD: $r = -0.48$, $P = 0.005$; and FA at an uncorrected threshold: $r = 0.38$, $P = 0.03$) and after correcting for self-reported trait impulsivity (MD: $r = -0.46$, $P = 0.009$; RD: $r = -0.50$, $P = 0.004$; and FA at an uncorrected threshold: $r = 0.37$, $P = 0.03$). MTR along the FS tract was not related to delay-discounting performance (neither to the AUC nor individual indifference points; *P*'s > 0.52).

Associations with Sex Steroid Hormones

Next, we performed correlation analyses between sex steroid levels, FS white matter integrity, and delay-discounting performance. Results showed that in males, higher salivary testosterone concentrations were related to a higher level of

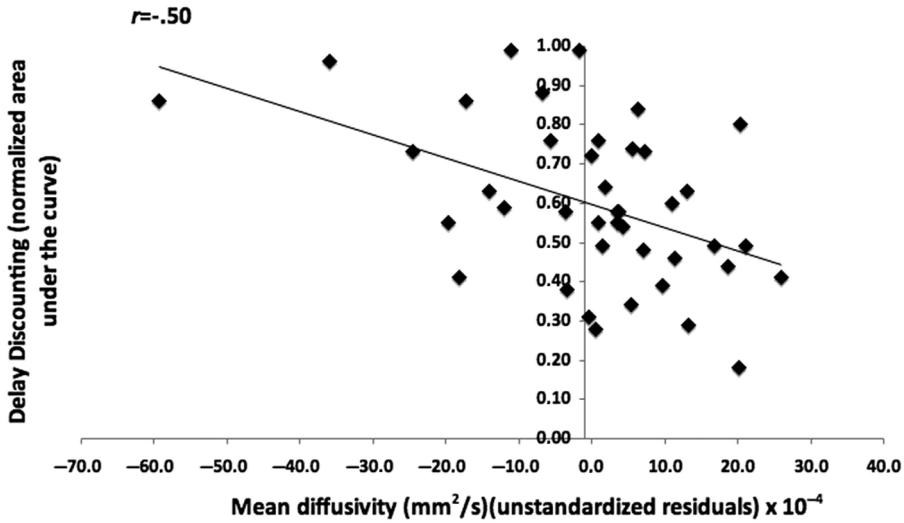

Figure 3. The higher MD within FS fiber tracts is associated with faster discounting. A smaller AUC means steeper discounting, hence an increased preference for (smaller) immediate rewards. Sex and age effects on MD are regressed out, and unstandardized residuals are displayed (a smaller value relates to lower MD). The correlation between AUC and FS MD is −0.50; $P = 0.001$.

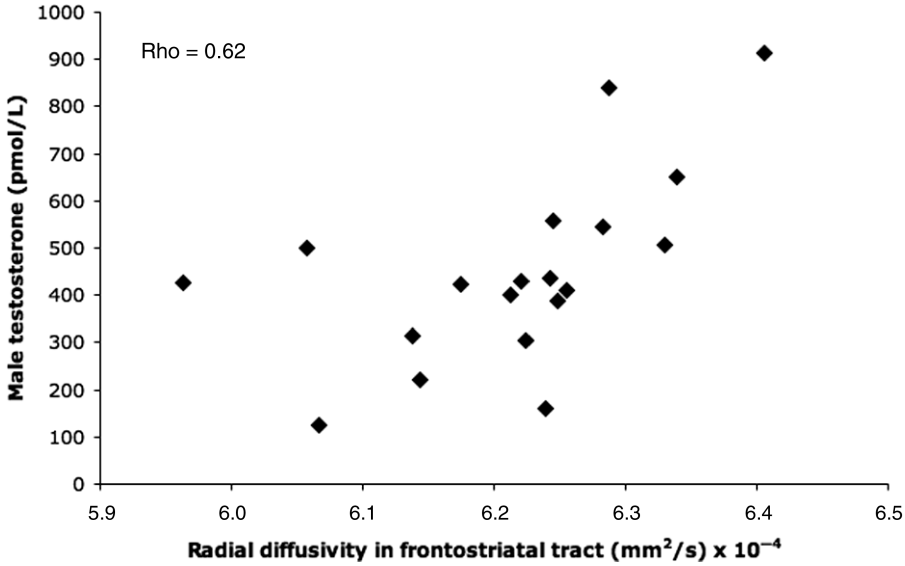

Figure 4. The association between testosterone and RD in males. The correlation between FS RD (in mm^2/s) and male testosterone: $\rho = 0.62$ ($P = 0.01$). Note that one outlier was removed from the male group (>3 SD; $N = 19$). Including this outlier in the analyses did not change the results.

radial diffusion in the FS tract ($\rho = 0.62$; $P = 0.005$; Fig. 4) and, related to lower FA at an uncorrected threshold ($\rho = -0.46$, $P = 0.05$). Salivary testosterone or estradiol concentrations in males were not associated with other FS white matter characteristics or delay-discounting performance.

In females, neither salivary estradiol nor testosterone concentration could significantly predict delay-discounting behavior or FS white matter integrity. Excluding the 4 non-contraceptive using females did not change the results.

Discussion

We investigated whether the quality of the FS white matter could predict individual differences in impulsive choice, measured by delay-discounting behavior. It was found that lower integrity within FS fiber tracts, measured by higher mean and RD and to a lesser extent by lower FA (i.e. at an uncorrected level), predicts steeper discounting of delayed monetary rewards. This association was found in both sexes, and was independent of age, intelligence, or self-reported trait impulsivity. An MTR signal, a putative measure of myelin, was not related to the impulsive choice. As a secondary more explorative goal, we investigated the possible contribution of sex steroid levels to white matter integrity within the FS tract, possibly explaining impulsive choices. In males, we report that a higher salivary testosterone concentration is associated with lower white matter integrity in the FS tract, measured by higher RD and lower FA. Sex steroid levels could not predict individual differences in delay-discounting behavior directly.

Impulsive behavior is a heterogeneous psychological construct (Evenden 1999) and its subtypes (e.g. impulsive action

and impulsive choice), are likely to be influenced by diverse neurobiological systems (Dalley et al. 2008; Pattij and Vanderschuren 2008). Delay discounting refers to the decline of the subjective value of rewards with increasing delay to reward, in which higher rates of discounting signify more impulsive choices. Steep rates of discounting, at an extreme, have been proposed to be a vulnerability factor to develop impulse control disorders (e.g. Reynolds 2006; Scheres, Tontsch, et al. 2010).

Earlier studies examining the impulsive choice using functional magnetic resonance imaging, reported the involvement of areas within the PFC and striatum (McClure et al. 2004; Peters and Büchel 2009; Sripada et al. 2011), brain areas suggested to be involved in coding of the subjective value of rewards (Peters and Büchel 2009) and self-control (Hare et al. 2009). However, merely localizing brain regions are not sufficient for understanding impulsive behavior, as our brain operates by way of interconnected networks. In an earlier study on delay-discounting behavior employing DTI in healthy subjects, steeper discounting was predicted by lower integrity (lower FA and higher MD) in white matter clusters within the frontal and temporal lobes (Olson et al. 2009). This study applied a so-called voxel-based technique, leaving the microstructural properties of the FS tracts unexplored. By using a tract-based approach, we now demonstrate for the first time that enhanced structural integrity of the white matter fiber bundles directly connecting the PFC with striatal brain regions relates to less impulsive choices. Using DTI, it is not possible to distinguish top-down (PFC controlling striatal systems) from bottom-up (striatum responses affecting PFC) processes. However, disrupting the (lateral) PFC, using transcranial magnetic stimulation, directly affected the preference for smaller immediate rewards over larger delayed rewards (Figner et al. 2010). That study provided causal evidence for prefrontal systems regulating impulsive decision-making. Thus, our results provide a neuroanatomical basis for the idea that a higher tendency toward immediate gratification results from less top-down control of the PFC over the striatal brain regions (Peters and Büchel 2011).

Interestingly, the ability to delay gratification is relatively stable across development (Casey et al. 2011). To the contrary, functional connectivity between the ventromedial PFC and ventral striatum contributing to individual differences in delay-discounting behavior still increases well into mid-adulthood (Christakou et al. 2011). Moreover, in a recent longitudinal DTI study in healthy subjects, it was reported that white matter development continues at least until early 30s (Lebel and Beaulieu 2011). Thus, even in our sample of young adults up to 25 years, there probably still is room for (processes influencing) axonal development.

From animal studies, it has become clear that white matter microstructural properties can be influenced by sex steroids (up to adulthood), by acting on glial cells (Melcangi et al. 2011), cells that produce myelin. In addition, developmental studies in human adolescents have reported an association between the large endogenous rise in sex steroid levels and white matter volume (Paus et al. 2010), density (Peper et al. 2008), and white matter microstructure (Herting et al. 2011). These studies suggest that internally fluctuating hormone levels might also contribute to the neural reorganization within the developing brain. In our (young) adult male sample, we were able to demonstrate that a higher morning salivary testosterone concentration relates to lower white matter integrity in the FS tract. Possibly, this effect can be explained by testosterone reducing axonal density within FS tracts, which would be in line with animal research reporting an increase in PFC dopaminergic axonal density after gonadectomy (blocking of testosterone production; Aubele and Kritzer 2011). However, based on our correlational data, we cannot infer causal effects of sex hormones. Therefore, these neurobiological explanations should be tested further in designs where hormonal levels are actually manipulated.

To examine white matter microstructure, we used a combination of 2 MRI techniques, DTI and MTI. DTI provides information on organization of white matter tracts, such as axonal alignment, axonal diameter, and myelinization (Le Bihan et al. 2001; Jones 2008). MTI allows for the study of the presence of macromolecules (Wolff and Balaban 1994), such as myelin (Schmierer et al. 2004), giving an important additional measure of white matter organization obtained through DTI. It remains to be explored though, which biological mechanisms are causing differences in white matter integrity, indexed with both imaging techniques. There are a number of possibilities. First, we report that MD, and mainly RD (diffusion perpendicular to axons) increases with more impulsive decision-making. This could imply that in higher delay aversive subjects, axons within the FS tract have a larger diameter. Indeed, in rats, it has been reported that a wider axons comprise higher RD than narrower ones (Barazany et al. 2009). Next to the axonal explanation, a second mechanism could be related to water content: In fast discounting subjects, there might be more bulk water around FS axons, leading to an increase in MD and/or RD. This could lead to water molecules moving more freely in general, and within the direction opposite to the alignment of axons in particular. Thirdly, our data indicated that lower FA is related to faster delay-discounting behavior (although this association did not survive a Bonferroni correction), pointing toward less myelin within the FS tract being implicated in more impulsive choices. However, the absent relation between impulsive behavior and MTR argues for axonal diameter rather than myelination within FS fibers driving individual differences in impulsive choice. Moreover, MTR signal appears not only susceptible to myelin, but also to (free) water content (i.e. water which is not bound within the axon, but can move freely; Vavasour et al. 2011). Thus, our data suggest that more impulsive choices are not primarily explained by the presence of less myelin or more bulk water within FS axons. The combination of all these axonal properties most likely contributes to the "integrity" of FS white matter, leading to individual differences in delay aversion, and, subsequently, to impulsive choice.

On the behavioral level, we could not observe a direct correlation between sex steroid hormones and impulsive choice. Sex hormones act on the brain through complex interactions with a variety of other hormones and neurotransmitters (Eisenegger et al. 2011; Kuhn et al. 2011). For instance, endogenous fluctuations in female estradiol affected PFC functioning during a working memory task, but the behavioral effect of estradiol depended on baseline dopamine status (Jacobs and D'Esposito 2011). It could therefore be argued that endogenous fluctuating hormonal levels only modestly mediate individual differences in behavioral output.

We were not able to demonstrate an association between sex steroid levels in females and white matter microstructure

within FS tracts. Although we controlled for diurnal hormone fluctuations and menstrual cycle (and excluded non-contraceptive using females), endogenous sex steroid concentrations are suppressed by the long-term contraceptive use (Merz et al. 2011). Possibly, contraceptive use could have masked an association between sex steroid levels in females and FS white matter microstructure. As examining, the relation between sex steroid hormones, FS white matter, and impulsive choice was not our primary aim and of exploratory nature only, replication of these data within larger samples is warranted.

With respect to neural correlates of pathological forms of delay aversion/impulsivity, lowered microstructural integrity within FS fiber tracts was previously found in ADHD (de Zeeuw et al. 2011) and autism spectrum disorder (Langen et al. 2011) when compared with healthy controls. In both pathologies, compromised integrity within this tract has been associated with decreased inhibitory control and enhanced reward sensitivity (Durston et al. 2011; Langen et al. 2011). Our data suggest that FS white matter integrity can also be used as a valid predictor of impulsive choice within the healthy population.

In conclusion, our study expands the understanding of the neural architecture of impulsive behavior. Individual differences in impulsive choice can, at least partially, be explained by the microstructural quality of FS pathways. Higher testosterone levels in males seem to lower the integrity within this tract. This study moved beyond the hypothesized relations between 2 crucial brain areas for impulse control, but demonstrated that the quality of the actual anatomical connection is predictive for individual differences in a healthy population. Myelination within FS white matter bundles might not be the driving force behind impulsive decision-making, but rather axonal density or caliber.

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Notes

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