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Cerebral White Matter Correlates of Delay Discounting in Adolescents

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Abstract

The adolescent brain undergoes extensive structural white matter (WM) changes. Adolescence is also a critical time period during which cognitive, emotional and social maturation occurs in transition into adulthood. Compared to adults, adolescents are generally more impulsive with increased risk-taking behaviors. The goal of this study is to examine whether adolescent impulsivity may be related to cerebral WM maturation. In 89 healthy adolescents, we assessed impulsivity using the delay discounting task, and MRI WM volumes in brain regions previously implicated in delay discounting behaviors. We found that smaller delay discounting AUC (area under the curve) was associated with larger WM volumes in orbitofrontal, dorsolateral and medial prefrontal cortices (PFC) and motor cortex. There were no significant effects of AUC on WM volumes within somatosensory brain regions. In our sample, younger age was significantly associated with greater WM volumes in orbitofrontal and dorsolateral PFC subregions. Even after accounting for age-related effects, preference for immediate rewards (or greater impulsivity) still correlated with larger WM volumes in prefrontal regions known to mediate cognitive control. Our findings lend further support to the notion that reduced brain WM maturity may limit the ability in adolescents to forgo immediate rewards leading to greater impulsivity.

Keywords

Addiction; Connectivity; Impulsivity; Neurodevelopment; Neuroimaging; MRI

1. Introduction

Impulsivity, regarded as dysfunctional inhibition of impulses (Hofmann, Friese, & Strack, 2009), encompasses a wide range of complex behavioral phenotypes (Evenden, 1999). One category of impulsive behaviors is the failure to consider future consequences when making decisions (Ainslie, 1975). This form of impulsivity is often assessed using the delay discounting task (de Wit, Flory, Acheson, McCloskey, & Manuck, 2007; Mitchell, 1999) (DDT). During DDT, test subjects are presented with a series of hypothetical forced-choice scenarios offering a smaller immediate reward over a larger but delayed one (e.g. Would you rather have \$2 now or \$10 in 180 days?). Delay discounting refers to the phenomenon where the current value of a future reward reduces as the delay to that reward increases. In animal

studies, lesions in the ventral striatum (Cardinal, Pennicott, Sugathapala, Robbins, & Everitt, 2001) or in specific regions within the orbitofrontal cortex (Mar, Walker, Theobald, Eagle, & Robbins, 2011; Mobini et al., 2002) have been shown to increase impulsivity. Although the rate of discounting provides a measure of impulsivity, DDT likely also entails decision-making, cognitive control and quantitative valuation of future rewards that are subserved by cortico-striatal and prefrontal brain networks. For example, McClure and colleagues have shown that greater BOLD signal changes in the ventral striatum, medial orbitofrontal, medial prefrontal, and cingulate cortices were associated with immediate monetary reward choices (McClure, Laibson, Loewenstein, & Cohen, 2004). On the other hand, delayed reward choices correlated with greater activations in the dorsolateral prefrontal cortex (PFC), motor cortex and somatosensory brain regions. These findings are therefore consistent with the notion that fronto-parietal regions exert cognitive control and top-down support (Bush, Luu, & Posner, 2000; Milham & Banich, 2005; Miller, 2000) over limbic brain structures that mediate reward evaluation (Ernst et al., 2005; Kuhn & Knutson, 2005; O'Doherty, Critchley, Deichmann, & Dolan, 2003; Peters & Buchel, 2010). Predominant prefrontal influence over limbic activation leads to "safe" behaviors while the converse may manifest as "risky" impulsive conduct (Cox et al., 2010; Miller & Cohen, 2001; Smith & Jonides, 1999). An imbalanced frontal-striatal interaction favoring the latter may bias toward the drive for immediate rewards, maladaptive decision-making and impulsivity.

The nodes within brain neural circuits subserving delay discounting (i.e. ventral striatum, prefrontal, medial orbitofrontal, anterior cingulate and parietal cortices) are interconnected by short and long white matter (WM) fiber tracts. Previous studies have examined brain WM correlates of delay discounting but findings have been mixed. Individuals with steeper delay discounting rates (or more impulsive) have smaller right prefrontal subgyral WM volumes and larger WM volumes in the right parahippocampus/hippocampus (Yu, 2012). Olson and colleagues found that greater impulsivity on the DDT correlated with lower WM tract integrity (i.e. lower fractional anisotropy (FA) and higher mean diffusivity (MD)) in diffuse brain regions corresponding to the inferior and superior longitudinal fasciculi, anterior thalamic radiation, uncinate fasciculus, inferior fronto-occipital fasciculus, corticospinal tract, and splenium of the corpus callosum (Olson et al., 2009). Olson and colleagues further reported that many of these impulsivity-WM tract associations (except in the right frontal and left temporal regions) were age-dependent suggesting that there are likely complex inter-relationships with adolescent brain maturation.

A hallmark of adolescence is accelerated remodeling of the brain leading to cognitive, emotional and social maturation. Changes in the adolescent brain include pruning of neuronal axons leading to thinning of prefrontal and parietal cortical gray matter (Giedd et al., 1999; Paus et al., 1999; Pfefferbaum et al., 1994; Sowell, Thompson, Holmes, Jernigan, & Toga, 1999; Sowell, Trauner, Gamst, & Jernigan, 2002). There is concurrent increased neuronal myelination associated with WM volume enlargements during adolescence which do not plateau until the fourth decade of life (Mathalon, Sullivan, Lim, & Pfefferbaum, 2001; Sowell et al., 2003). Adolescents are frequently perceived to be more impulsive and prone to engage in increased risk taking leading on to drug use, car accidents and unprotected sexual activity (Arnett, 1992). Adolescent predisposition to impulsivity is thought to be related to a "maturational gap" (Casey, Getz, & Galvan, 2008; Nelson et al.,

2002); such that the relatively late maturing prefrontal-based control brain regions are inadequate in regulating the earlier maturing frontostriatal reward circuits (Fuster, 2002). An emerging body of literature supports the view that WM maturation during adolescence increases the efficiency of prefrontal inhibitory interactions on the striatum, and may underlie reductions in impulsivity as adolescents progress into adulthood (Berns, Moore, & Capra, 2009; van den Bos, Rodriguez, Schweitzer, & McClure, 2015).

The goal of this study is to investigate the relationships between cerebral WM volumes and delay discounting rates so as to assess how WM maturation during adolescence may correlate with variability in impulsivity. We hypothesize that reduced maturity in WM connecting brain regions known to mediate delay discounting behaviors will be associated with preference for immediate rewards.

2. Materials and methods

2.1. Sample

Of the 99 adolescents (aged 12–17 years) recruited from the community through advertisements, 10 subjects (M:F=3/7) did not have valid delay discounting data (see below) and were omitted from further analyses leaving 89 adolescents (Table 1) in the current study. Participants and their parents/legal guardians gave written informed consent approved by the University of Iowa Human Subjects Institutional Review Board. All subjects were assessed using the CAPA (Child and Adolescent Psychiatric Assessment, Child Interview (Angold, Cox, Prendergast, Rutter, & Simonoff, 2008)), a semi-structured interview instrument to rule out lifetime history of psychiatric or substance use disorders. Participants with intellectual disability (WRAT3 Reading Score (Wilkinson, 1993) <30), serious medical/neurological disorders or contraindications for magnetic resonance imaging were also excluded. Sociodemographic characteristics of the sample are summarized in Table 1. The sample comprised predominantly of right-handed (85.4%) Caucasians (92.1%) in mid-adolescence (Mean age=14.4 years (SD=1.32)) with approximately equal gender distribution (48.3% males).

2.2. Delay Discounting Task (DDT)

The DDT was based on an experimental paradigm previously developed by Richards and colleagues (Richards, Zhang, Mitchell, & de Wit, 1999). It was administered on a computer monitor screen. The software program controlling the DDT was written in Inquisit scripting language installed on Inquisit 4 Lab software (Version 4.0.3; Millisecond Software LLC, Seattle, Washington) running Windows 7 operating system. In our computerized DDT, subjects chose between a series of two hypothetical monetary rewards, i.e. a smaller (ranging \$0.50 to \$10) immediately available reward versus a \$10 standard reward in the future (2, 30, 180 or 365 days later). Detailed task instructions appeared onscreen. Each study participant was supervised by a research team personnel verifying that the participant had understood the experimental task. Before starting the DDT, subjects were also told that they would receive a cash reward based on one of their answers but that the reward would be chosen randomly by the computer program.

The DDT script used a random adjustment algorithm to determine an indifference point for each of the 5 different delays (i.e. 0, 2, 30, 180 and 365 days). Area under the curve (AUC) and discounting constant k were then derived based on the indifference point at each delay to the standard \$10 reward. AUC was calculated by summing the resulting trapezoids (Myerson, Green, & Warusawitharana, 2001) while discounting constant k calculation used a nonlinear regression least-squares fit approach. Smaller AUC or larger k indicate preference for immediate rewards or higher impulsivity (Myerson et al., 2001). Similar results were found regardless of whether AUC or natural log-transformed k (due to its skewed distribution) was used in the statistical analyses. Because AUC provides a more straightforward interpretation of discounting behavior that is not linked to a specific theoretical framework (Myerson et al., 2001), only AUC findings will be presented in this report. Results based on log-transformed k are available in the Supplemental Materials Section.

Consistent discounting behavior was defined as having at least two decreases and not more than one increase in indifference points as time increased (Dixon, Marley, & Jacobs, 2003). A proportion of study participants inevitably do not show discounting behavior, i.e. their indifference points do not consistently decrease with increased time to reward delivery. As with previous studies (Dixon et al., 2003; Reynolds, Richards, & de Wit, 2006), subjects ($N=10$) who did not show consistent discounting behavior were excluded leaving 89 study participants who had valid discounting data. Subjects with versus without valid delay discounting did not differ significantly on age, gender distribution, race, handedness, education, parental education or AUC ($p > 0.13$).

2.3. Brain MR image acquisition and processing

Each participant underwent a brain MRI scan on the same day the DDT was administered. High-resolution, multimodal imaging of the whole brain was obtained in a single scanning session using a research-dedicated Siemens 3-Tesla TIM Trio scanner equipped with a 12-channel head coil. Each scan included T1-weighted images which were obtained using a 3D coronal MP-RAGE sequence with the following imaging parameters: TE=2.8ms, TR=2530ms, TI=900ms, FOV=256×256×220 mm, Matrix=256×256×220, flip angle=10°, Bandwidth=180 Hz/Px, Averages=1, iPat=2.

After the MR scans were acquired, the images were transferred to our Image Processing Lab. FreeSurfer software (Dale, Fischl, & Sereno, 1999; Fischl, Sereno, & Dale, 1999), which was used to process T1-weighted images for the current study, comprised of 3 automated stages. The output images from FreeSurfer automated processing were reviewed by an image analyst looking for errors in template registration, skull strip, segmentation and parcellation, and manually edited where necessary. The steps involved in FreeSurfer image processing included motion correction, removal of non-brain tissue, Talairach transformation, segmentation of subcortical white matter and deep gray matter structures, tessellation of gray matter-white matter boundary, automated topology correction, gray matter, white matter and CSF tissue classification, and parcellation and labeling of the cortical gray mantle based on atlas and exemplar traces (Desikan et al., 2006; Fischl et al., 2004).

Cerebral white matter (WM) subregions corresponding to the parcellated cortical gray mantle were delineated as previously described (Fjell et al., 2008; Salat et al., 2009). In brief, a Voronoi polygon in the WM voxels of the MR volume was constructed based on distance to the nearest cortical gray mantle parcellation label and by limiting the label expansion to no more than 5 mm. Each Voronoi polygon was then assigned the label of the parcellation unit to derive volume measures of the cerebral WM underlying the cortical gyral and sulcal areas (Salat et al., 2009).

2.4. Statistical analysis

Statistical analyses were conducted in stages to reduce Type I error which may arise from multiple comparisons. To assess impulsivity-WM brain volume relationships, we first tested the effects of delay discounting AUC on 5 regions of interest (ROIs) previously implicated in delay discounting, i.e. orbitofrontal cortex, dorsolateral prefrontal cortex (PFC), medial PFC, motor cortex, and primary somatosensory and association cortices. An omnibus MANCOVA test simultaneously assessed the relationships between AUC and the constituent FreeSurfer parcellated WM regions within each ROI (see Table 2). Orbitofrontal ROI comprised of FreeSurfer WM subregions underlying lateral orbitofrontal gyrus, medial orbitofrontal gyrus and pars orbitalis. Similarly, the constituent FreeSurfer WM volume measures within the dorsolateral PFC ROI were rostral middle frontal gyrus, pars opercularis and pars triangularis; medial PFC ROI: superior frontal gyrus, rostral anterior cingulate and caudal anterior cingulate; motor cortex ROI: precentral and caudal middle frontal gyri; primary somatosensory and association cortices ROI: postcentral, supramarginal and inferior parietal gyri. In each MANCOVA omnibus test, the constituent FreeSurfer parcellated WM regions were entered simultaneously as dependent measures. AUC was the independent measure. Covariates included in the MANCOVA omnibus test were total cerebral WM volume, gender and age. Age-related differences in cerebral WM volumes during adolescence have previously been shown to differ between gender (De Bellis et al., 2001). If the omnibus test was statistically significant ($p < .05$), post hoc univariate analyses of that ROI's constituent FreeSurfer parcellated WM regions were then performed. In these univariate analyses, each FreeSurfer parcellated WM volume was the dependent measure, AUC the independent measure, and covariates were again total cerebral WM volume, gender and age. To further minimize Type I errors, these univariate analyses used the adaptive false discovery rate (FDR) procedure (Benjamini & Hochberg, 2000) to adjust for multiple comparisons. All WM volumes were derived by summing the left and right hemispheric measures.

3. Results

Of the five ROIs previously implicated in delay discounting, there were significant main effects of AUC on WM volumes within 4 ROIs: orbitofrontal cortex, dorsolateral PFC, medial PFC and motor cortex (Table 2; $F = 3.22$, $p = 0.03$). Main effects of delay discounting on somatosensory ROI were not statistically significant ($F = 1.97$, $p = 0.13$). Post hoc univariate analyses found significant main effects of AUC on most constituent FreeSurfer parcellated WM volumes (FDR-corrected $p = 0.03$; Table 2) except for rostral anterior cingulate and caudal anterior cingulate (FDR-corrected $p = 0.26$). AUC was inversely

correlated with WM volumes (Table 2 and Figure 1; Pearson partial r ranged between -0.34 to -0.24 ; Median= -0.31). Preference for immediate rewards (or greater impulsivity) was associated with larger WM volumes after accounting for the effects of global brain WM volume, gender and age.

Main effects of AUC on total cerebral WM volume were not statistically significant ($F=0.02$, $p=0.90$). AUC did not differ significantly between males versus females (Mean= 0.54 ($SD=0.31$) and 0.59 ($SD=0.29$) respectively, $T=0.77$, $p=0.45$). AUC was weakly correlated with age (Pearson $r=0.25$, $p=0.02$) where younger age was associated with preference for immediate rewards. There were no statistically significant main effects of age on most WM ROIs (Table 2; $F=2.59$, $p=0.08$); except for orbitofrontal and dorsolateral PFC only ($F=2.67$ and 3.05 respectively, $p=0.05$) wherein younger subjects had larger constituent FreeSurfer parcellated WM volumes (partial r ranged between -0.36 to -0.24 ; Median= -0.26). When the MANCOVA omnibus tests were repeated using only right-handed subjects ($N=76$), results were similar to those involving the entire sample (available upon request). To explore whether delay discounting was lateralized to one brain hemisphere versus the other, left and right FreeSurfer WM volumes were simultaneously entered as repeated-measures dependent variables (Table 3). There were no statistically significant main effects of AUC-by-side interaction on WM volumes ($F=1.95$, $p=0.17$; except for superior frontal WM volume ($F=4.55$, $p=0.04$)) suggesting that the relationships between WM volumes and delaying discounting were generally similar in the left and right hemispheres.

4. Discussion

In this study, we examined brain white matter (WM) correlates of delay discounting behaviors in a large sample of healthy adolescents. We found that larger WM brain volumes within prefrontal (orbitofrontal, medial and dorsolateral) and motor cortices were associated with preference for immediate rewards. Younger adolescents also preferred immediate rewards. Even after accounting for age-related effects, greater impulsivity still correlated with larger WM volumes in cortical brain regions known to mediate delay discounting. Within the age range of our sample (12–17 years), younger adolescents (with its corollary of being developmentally less mature) tended to have larger WM brain volumes in orbitofrontal and dorsolateral PFC; brain regions vital for cognitive control and higher level deliberative processes. When the inter-relationships between age, WM volumes and delay discounting performance are viewed together, our findings would be consistent with the notion that reduced brain WM maturity may limit the ability in adolescents to forgo immediate rewards leading to greater impulsivity. We did not find cerebral hemispheric laterality in conferring delay discounting.

Cerebral WM regions we examined in this study comprised of short association fibers, long association fibers and projection fibers. Short association fiber tracts (also known as “U” fibers) run just below the deepest parts of the sulci and connect adjacent gyri. Long association fibers (including the superior longitudinal fasciculus, middle longitudinal fasciculus, inferior longitudinal fasciculus, uncinate fasciculus, frontal aslant tract, vertical occipital fasciculus) link different lobes within the same hemisphere. Projection fiber tracts (including the internal capsule, frontal-accumbens fasciculus, socallosal fasciculus, corona

radiate and optic radiations) connect the cerebral cortices to basal ganglia, brainstem and spinal cord.

The functional significance of larger WM brain volumes remains uncertain even though larger WM volumes most frequently connotes a “healthier” state. Individuals with neuropsychiatric disorders have been shown to have brain volume abnormalities. For example, schizophrenia patients are more likely to have smaller cerebral WM volumes than matched unaffected comparison subjects (Wright et al., 2000), and smaller WM volumes have been associated with greater symptom severity, poorer cognition and functional outcome (Davis et al., 2003). Among individuals with autism and related disorders, on the other hand, aberrant WM volume enlargements may be restricted to specific developmental stages (Courchesne et al., 2001); highlighting the importance of dynamic brain volume changes during brain maturation and how these may be related to neurodevelopmental disorders and cognition. In studies investigating delay discounting, preference for immediate rewards have been associated with indicators of reduced brain maturity, including smaller prefrontal WM volumes (Yu, 2012), smaller lateral frontal gray matter volumes (Bjork, Momenan, & Hommer, 2009), and lower FA (fractional anisotropy) and higher MD (mean diffusivity) within frontotemporal regions (Olson et al., 2009). In contrast, Berns and colleagues reported an opposite pattern where more mature frontal WM (higher FA) was associated with questionnaire-based self-reports of risky behaviors (Berns et al., 2009). Such delay discounting-brain maturity associations are predicated on current understanding regarding WM developmental trajectories.

During adolescence and early adulthood, there is increased neuronal myelination associated with WM volume enlargements (Mathalon et al., 2001; Sowell et al., 2003). Such WM volume changes show regional specificity progressing from posterior to anterior brain regions with frontal lobes achieving maximum volumes during the 4th or 5th decade of life (Giedd et al., 1999; Paus et al., 1999; Pfefferbaum et al., 1994; Sowell et al., 1999). While most cross-sectional studies in adolescents have reported positive correlations between age and WM volumes (e.g. (Tamnes et al., 2010)), other investigators have found either negative (Nagel et al., 2006; similar to what we found), both positive and negative (Taki et al., 2013) or no significant (Whitford et al., 2007) correlations between age and frontal WM volumes. In a recent review of the literature regarding within-subject longitudinal brain volume changes across the human life span (Hedman, van Haren, Schnack, Kahn, & Hulshoff Pol, 2012), the authors found that most studies (including those involving adolescents) assessed developmental changes based on study samples with restricted age ranges and/or over relatively short longitudinal follow-up durations. Such limitations may explain in part the variability and inconsistencies in age-related WM volume changes reported across different studies and in the current study. Additional research involving adolescents are still needed to firmly establish the developmental trajectory of WM brain volumes.

In the current study, age-WM volume relationships we observed run counter to most previous studies. We did not find significant main effects of age on WM volumes in the majority of ROIs we examined, including medial PFC, motor cortex or primary somatosensory and association cortices. Only within the orbitofrontal and dorsolateral PFC were there statistically significant relationships between age and WM volumes. Within the

restricted age range of our sample (12–17 years), such associations were weak to moderate inverse correlations with younger subjects being more likely to have larger WM volumes in the orbitofrontal and dorsolateral PFC. Younger age was also weakly correlated with smaller AUC delay discounting (or preference for immediate rewards). Nonetheless, even after controlling for the effects of age in our statistical models, greater impulsivity still correlated significantly with larger WM volumes in cortical brain regions known to mediate delay discounting, especially in the orbitofrontal and dorsolateral PFC. This suggests that weak patterns of developmental dysmaturation may mediate delayed discounting deficits. Even though our findings are internally consistent and are in keeping with previous reports associating reduced brain maturity with preference for immediate rewards (Bjork et al., 2009; Olson et al., 2009; Yu, 2012), the directionality of correlations between larger orbitofrontal and dorsolateral PFC WM volumes with younger age and with preference for immediate rewards needs to be interpreted with caution.

The prefrontal cortex has been shown to regulate cognitive control and executive functions (Bush et al., 2000; Cabeza & Nyberg, 2000; Milham & Banich, 2005; Miller, 2000) providing top-down regulation of the ventral striatum in reward processing (Ernst et al., 2005; Kuhnén & Knutson, 2005; O'Doherty et al., 2003; Peters & Buchel, 2010). Dysfunction in prefrontal brain regions may therefore lead to reduced ability to resist immediate rewards; serving as a risk factor for impulse control disorders (Goldstein & Volkow, 2002). In the developing adolescent brain, differential maturation of hedonic drive processes (i.e. relatively late prefrontal maturation compared to earlier maturation of the limbic structures) may underlie the greater propensity of adolescents (versus adults) to engage in risk taking behaviors (Galvan et al., 2006). In a recent study, van den Bos and colleagues reported that diminished prefrontal-striatal connectivity related to adolescent brain maturation was associated with impatience as assessed by delay discounting (van den Bos et al., 2015). These findings provide further support that adolescent WM maturation plays an important role in mediating impulsive behaviors.

Several limitations of our study need to be considered when interpreting our results. First, our study sample comprised of adolescents within a relatively restricted age range. As opposed to a wider spread in age (e.g. 9–23 years in (Olson et al., 2009)), having study participants who are only between 12–17 years of age in the current study may have in part led to finding an inverse WM volume-age relationship in the orbitofrontal and dorsolateral PFC regions, the absence of significant relationship with age for the other WM brain regions, and the weak correlations between younger age and greater impulsivity. The age of our study participants may have also contributed to our results of nonsignificant main effects of delay discounting on WM volumes in the somatosensory cortices. Although these regions have been previously implicated as part of the neural circuits mediating delay discounting (Ernst & Paulus, 2005; Louie & Glimcher, 2010), the somatosensory cortices mature earlier and achieve maximum WM volumes during childhood (Deoni, Dean, Remer, Dirks, & O'Muircheartaigh, 2015) before the age at which MRI brain scans were obtained in our study sample.

Second, given the cross-sectional study design, interpretations relating to brain maturation need to be viewed with caution. Age-brain volume relationships provide a measure for brain

developmental changes. But such age-brain volume associations could be spurious arising from correlations with third factor not measured in the current study, and may have little or no meaning with respect to brain maturation. In the current statistical analyses, we have carefully assessed for potential spurious factors such as overall head size (total cerebral WM volume) and have minimized Type I errors (by performing analyses in stages, i.e. omnibus MANCOVA tests as the first cut and with follow-up univariate tests correcting for multiple comparisons only if the initial MANCOVA is statistically significant). In future analyses, we will be able to assess adolescent brain maturational changes when our study sample returns for repeat follow-up assessments of MRI scans and delay discounting testing.

Third, even though FreeSurfer provides equivalent accuracy as other widely used brain volumetry methods in estimating WM volumes (Klauschen, Goldman, Barra, Meyer-Lindenberg, & Lundervold, 2009), the validity of FreeSurfer WM volume measures remains uncertain. These FreeSurfer derived WM measures consist of short association fibers, long association fibers and projection fibers connecting the overlying gray matter mantle with adjacent gyri or with more distant brain regions within or between cerebral hemispheres. Future studies may explore other methodologies in assessing WM such as tractography or diffusion-weight imaging.

Fourth, there are no widely accepted ways to group subregions within the prefrontal cortex; based either on cytoarchitectural characteristics, functional cognitive processes or connections with other brain regions. Although the prefrontal cortex has been shown to subserve distinct cognitive processes (including reward evaluation and decision-making), prefrontal subregions also mediate multiple memory systems and error detection in guiding a wide variety of behaviors and adaptive responses (Euston, Gruber, & McNaughton, 2012; Rushworth, Buckley, Behrens, Walton, & Bannerman, 2007; Rushworth, Noonan, Boorman, Walton, & Behrens, 2011). In the current study, we have grouped superior frontal, rostral anterior cingulate and caudal anterior cingulate subregions as medial PFC ROI. Although we found significant main effects of delay discounting on this medial PFC ROI, post hoc univariate analyses of its constituent WM subregions indicated that only superior frontal WM volume (but not rostral anterior cingulate or caudal anterior cingulate subregions) was significantly associated with delay discounting behaviors. The nonsignificant relationships with anterior cingulate WM volume measures could potentially be related to the fact that even though the anterior cingulate cortex has been involved in delay discounting behaviors (Kuhnen & Knutson, 2005; McClure et al., 2004; O'Doherty et al., 2003; Peters & Buchel, 2010; Rushworth et al., 2011), it is also implicated in several other forms of memory and learning (Euston et al., 2012; Rushworth et al., 2007).

Lastly, although delay discounting provides a useful construct to study impulsivity, DDT also involves other neural processes including those that mediate reward evaluation and cognitive control. We have limited the current analyses to prefrontal lobe given its role in executive control and in impulse inhibition. In future studies, investigators may broaden the focus beyond impulsivity so as to also assess the other dimensions (such as reward processing, decision-making and cognitive control) that the DDT taps into.

5. Conclusion

This study provides additional evidence that white matter volumes within prefrontal brain regions are associated with individual differences in delay discounting. Relative immaturity in prefrontal white matter may reduce executive control over limbic regions important in mediating reward processing thereby leading to increased impulsivity among adolescents.

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(A) Orbitofrontal Cortex

(B) Dorsolateral & Medial PFC

(C) Motor Cortex

Figure 1.

FreeSurfer brain white matter segmentation with scatterplots of white matter volume (cubic centimeters)-delay discounting (AUC, area under curve) relationships (partial Pearson correlation coefficient (r); covariates: total cerebral WM volume, gender and age). (A) Orbitofrontal ROI (region of interest) comprising of medial orbitofrontal gyrus, lateral orbitofrontal gyrus and pars orbitalis. (B) Dorsolateral prefrontal cortex (PFC) ROI (comprising of rostral middle frontal gyrus, pars opercularis and pars triangularis) and Medial PFC ROI (comprising of superior frontal gyrus, rostral anterior cingulate and caudal anterior cingulate) (C) Motor cortex ROI (comprising of caudal middle frontal and precentral gyri).

Table 1

Sociodemographic characteristics of 89 adolescent subjects with valid delay discounting

Mean age (years (SD))	14.4 (1.32)
Sex (M/F (% Males))	43/46 (48.3)
Race (% Caucasian)	92.1
Handedness (R/L/Mixed (% Right))	76/1/12 (85.4)
Mean educational level (grade (SD))	8.2 (1.49)
Mean parental education (years (SD))	15.2 (2.31)
Mean delay discounting (AUC proportion (SD))	0.49 (0.29)

Table 2

Relationships between delay discounting (AUC) and MRI brain white matter (WM) volumes in 89 adolescents: Omnibus MANCOVA¹ and univariate analyses²

Region of Interest	MANCOVA (F (p))		FreeSurfer Gyral Labels	Univariate Analyses			
	AUC	Age		F	Raw p	FDR p	r
Orbitofrontal Cortex	4.12 (.01)	2.67 (.05)	Lateral Orbitofrontal	10.68	0.002	0.012	-0.34
			Medial Orbitofrontal	7.54	0.007	0.017	-0.29
			Pars Orbitalis	8.67	0.004	0.012	-0.31
Dorsolateral PFC	3.72 (.01)	3.05 (.03)	Rostral Middle Frontal	9.15	0.003	0.012	-0.31
			Pars Opercularis	9.09	0.003	0.012	-0.31
			Pars Triangularis	5.25	0.024	0.031	-0.24
Medial PFC	3.22 (.03)	1.04 (.38)	Superior Frontal	8.68	0.004	0.012	-0.31
			Rostral Anterior Cingulate	1.38	0.244	0.263	-0.13
			Caudal Anterior Cingulate	0.43	0.516	0.516	-0.07
Motor Cortex	3.49 (.03)	2.59 (.08)	Precentral	6.97	0.009	0.019	-0.28
			Caudal Middle Frontal	5.86	0.018	0.031	-0.26
Primary Somatosensory & Association Cortices	1.97 (.13)	1.62 (.19)	Postcentral	-	-	-	-
			Supramarginal	-	-	-	-
			Inferior Parietal	-	-	-	-

¹Multivariate analysis of covariance (MANCOVA): Omnibus test assessing main effects of area under the curve (AUC) measure and subject age on each WM brain region of interest (ROI) (covariates: total cerebral white matter volume and gender; summed left and right hemispheric WM volumes).

²For omnibus tests which were statistically significant ($p<.05$), post hoc univariate analyses tested the main effects of AUC on each constituent FreeSurfer parcellated WM volume (Raw p: unadjusted p-value; FDR p: p-value derived from adaptive false discovery rate (FDR) procedure; r: Pearson partial correlation coefficient; covariates: total cerebral WM volume, gender and age).

Table 3

Repeated-measures ANCOVA exploratory analyses¹ to assess whether the effects of delay discounting on white matter volumes may be lateralized to one cerebral hemisphere.

FreeSurfer White Matter Volume Measure	AUC*Side ¹ F (p)	Left ² F(p)	Right ² F (p)
Lateral Orbitofrontal	0.39 (0.53)	6.92 (0.01)	9.49 (0.003)
Medial Orbitofrontal	1.46 (0.23)	8.07 (0.006)	2.37 (0.13)
Pars Orbitalis	0.20 (0.65)	5.23 (0.02)	6.49 (0.01)
Rostral Middle Frontal	0.66 (0.41)	4.71 (0.03)	9.71 (0.003)
Pars Opercularis	0.06 (0.80)	7.64 (0.007)	7.40 (0.008)
Pars Triangularis	0.66 (0.42)	2.74 (0.10)	6.13 (0.02)
Superior Frontal	4.55 (0.04)	4.94 (0.03)	11.10 (0.001)
Rostral Anterior Cingulate	0.01 (0.91)	0.32 (0.57)	0.41 (0.52)
Caudal Anterior Cingulate	1.95 (0.17)	0.07 (0.79)	2.35 (0.13)
Precentral	0.60 (0.44)	6.66 (0.01)	5.14 (0.03)
Caudal Middle Frontal	1.08 (0.30)	3.45 (0.07)	7.68 (0.007)

¹ Analysis of covariance (ANCOVA): For each FreeSurfer white matter (WM) volume measure, its corresponding left and right hemispheric WM volumes were simultaneously entered as repeated-measures dependent variables in the general linear statistical models. Delay discounting (area under the curve (AUC)) measure, side and AUC-by-side interaction term (AUC*side) were the independent measures (covariates: total cerebral WM volume, age and gender). Statistically significant AUC*side interaction would suggest that the relationships between WM volume and AUC differed significantly between left and right cerebral hemispheres.

² Univariate analyses of individual hemispheric (left or right) FreeSurfer WM volume and delay discounting AUC measure (covariates: total cerebral WM volume, gender and age).