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White matter correlates of temporal discounting in older adults

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Abstract

Temporal discounting, the tendency to select a smaller reward offered sooner over a larger reward offered at a later time, has been associated with a number of real-world decision-making outcomes important for health and wellbeing. Neurobiological mechanisms supporting temporal discounting have been explored among younger participants, and these have considered white matter integrity. However, the white matter correlates of temporal discounting in older adults are unclear. We hypothesized that greater temporal discounting would be associated with poorer white matter integrity measures, more specifically lower fractional anisotropy and higher trace, in older adults. Participants were 302 older persons without dementia (mean age = 81.38, mean years of education = 15.75, 75.5% female, mean MMSE = 28.29) from the Rush Memory and Aging Project, a community-based longitudinal study of aging. Temporal discounting was assessed using standard elicitation questions. White matter integrity was assessed with diffusion tensor imaging (DTI). Regression models were adjusted for the effects of age, sex, education, and white matter lesions.

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Conflict of interest The authors declare that they have no conflict of interest.

Ethical statement All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Secondary models further adjusted for global cognition. Results revealed significant associations between temporal discounting and white matter integrity measures (FA and trace) in bilateral frontal, frontostriatal, and temporal–parietal lobe white matter tracts, and results remained significant after further accounting for global cognition. These results suggest that temporal discounting is inversely associated with white matter integrity in old age and that this association is independent of global cognition.

Keywords

Temporal discounting; Trace; Fractional anisotropy; White matter; Diffusion tensor imaging; DTI

Introduction

Temporal discounting is a concept from the field of behavioral economics that refers to the tendency to prefer a more immediate and smaller reward over a larger reward offered at a later time [see Frost and McNaughton (2017), and Vanderveldt et al. (2016), for reviews]. This tendency reflects a form of decision-making impulsivity, or more specifically, a difficulty in appreciating the greater value of future events in comparison to the value of current events (Reynolds and Schiffbauer 2005). Temporal discounting has been associated with a number of negative real-world decision-making outcomes such as obesity (McClelland et al. 2016), substance abuse (Moody et al. 2016), risky sexual behavior (Herrmann et al. 2015), and lower income (Reimers et al. 2009) though most temporal discounting studies have been conducted with younger samples, and little is known about temporal discounting in older adults. Older adults are at higher risk for poorer decision-making due to age-associated brain changes, and in old age, temporal discounting can have profound financial and health consequences, resulting in decreased wellbeing and independence. We previously demonstrated that temporal discounting is associated with poorer cognitive function (Boyle et al. 2012), cognitive decline (James et al. 2015), and mortality (Boyle et al. 2013). To date, however, the neural underpinnings of temporal discounting in old age remain unclear. A greater understanding of the neural mechanisms may facilitate interventions or strategies for better decision-making in old age.

In earlier work using resting-state functional magnetic resonance imaging (fMRI), we showed that functional connectivity of brain structures was associated with temporal discounting in old age (Han et al. 2013). Specifically, we observed that functional connectivity of the right parahippocampal cortex to frontoinsula seed regions of interest was associated with lower temporal discounting, and functional connectivity of ventromedial prefrontal cortex structures to frontoinsula seed regions was associated with higher temporal discounting. Our functional connectivity findings are consistent with previous work observed in younger ages (e.g., Ballard and Knutson 2009), and support the importance of memory network integrity in old age. This understanding is consistent with a model of temporal discounting that posits memory network brain structures involved in prospective imagery may interact with frontal-based valuation structures as a system for decision-making (Peters and Buchel 2011). Because functional connectivity measures can be at least partially dependent on the integrity of structural white matter connections that

facilitate communication between gray matter regions, we hypothesized that temporal discounting would be associated with white matter structural integrity. Associations of temporal discounting with measures of white matter integrity between frontal and other brain regions have been observed in younger populations (Olson et al. 2008; Peper et al. 2013; Van den Bos 2014); however, whether and to what extent these associations hold in old age is less known. Furthermore, no study to our knowledge has considered the contributions of global cognition to these associations.

Using diffusion tensor imaging (DTI), we tested the hypothesis that higher temporal discounting is associated with poorer white matter integrity indicators in regression models that adjusted for the impact of age, sex, education, and white matter hyperintensities. We additionally examined whether results remained significant after further adjusting for cognitive function. One prior study investigated temporal discounting associations with DTI measures using a set of predefined regions of interest in 40 healthy older adults (Hanggi et al. 2016). We investigated this using a voxelwise whole-brain approach in more than 300 older adults without dementia from the Rush Memory and Aging Project, a longitudinal clinicopathologic study of aging. To our knowledge, this is the largest study of temporal discounting associations with white matter integrity in older adults without dementia, and the only DTI study of temporal discounting that has considered the contribution of global cognition.

Materials and methods

Experimental design

Participants—The Rush Memory and Aging Project is a clinical–pathologic community-based longitudinal study of aging and dementia (Bennett et al. 2012), and participants of the present temporal discounting and diffusion tensor imaging study were drawn from this larger study. Retirement homes, senior housing facilities, residential facilities, and Chicago-based community organization are sources of recruitment for the Rush Memory and Aging Project. Participants submit to clinical evaluations annually and were screened for dementia according to well-established criteria (Bennett et al. 2002, 2006). First, an experienced neuropsychologist with expertise in Alzheimer’s disease (AD) and blinded to participant age, sex, and race reviewed all results of cognitive measures and rendered a clinical judgment as to cognitive impairment after reviewing data on education, sensory deficits, and motor deficits. Second, a clinician with expertise in the diagnosis of AD reviewed all available participant information (brain scan, medical history, cognitive data, neurological exam) and rendered a clinical judgment as to whether the information was consistent with dementia according to NINCDS/ADRDA criteria (McKhann et al. 1984).

The Rush Memory and Aging Project has been continuously enrolling since 1997. A sub-study focused on decision-making in old age that had the temporal discounting measure began in 2010. Neuroimaging of participants began in 2009. At the time of the analyses described in this study, 1803 participants had completed the baseline data collection of the parent study (Rush Memory and Aging Project) and 975 of these participants were enrolled in the decision-making sub-study. Of these 975 participants, 383 had DTI data at the time of these analyses. However, 40 scans failed quality control, leaving 343 with usable DTI data.

Of these 343 participants with valid DTI data, 5 had dementia and 36 had missing covariate data, leaving a total of 302 participants without dementia who completed the temporal discounting measure and DTI.

Temporal discounting—The method for quantifying temporal discounting has been described previously (Boyle et al. 2012). To briefly review, there were 7 questions posed that took the form: “Would you prefer \$10 in cash right now or [one of seven amounts] in a month?” The amounts used were \$14, \$20, \$15, \$11, \$18, \$13, and \$30. The delay period was fixed at 1 month. The discounting factor, α , was estimated using a hyperbolic function (Laibson 1997):

$$V = \frac{A}{1 + \alpha D}, \quad (1)$$

where V represents the discounted value of A , the future reward, at D , the delay. Smaller values of α represent lower discounting, resulting in larger values of V .

If Y is the observed outcome of a trial, the decision to choose a reward at a later time is represented by $Y = 1$, and the current reward decision choice is $Y = 0$, we hypothesized that the probability $P(Y = 1)$ depends on the difference between the discounted future reward V and the present reward C . The odds, therefore, of choosing the future reward over the present reward can be described as

$$\frac{P(Y = 1)}{P(Y = 0)} = e^{V - C}. \quad (2)$$

For example, if $V - C = 0$, this would represent no difference between the delayed and current rewards. If $V - C$ is positive, this would represent a delayed reward preference with odds greater than 1. If $V - C$ is negative, this would represent an immediate reward preference. The discounting rate α is thus determined from Eq. (2).

Cognition—A board-certified clinical neuropsychologist supervised the administration of a battery of cognitive measures. These measures evaluated a broad range of cognitive performance abilities as previously reported (Bennett et al. 2012). This cognitive battery included measures of visuospatial ability (Judgment of Line Orientation and Standard Progressive Matrices), perceptual speed (oral version of the Symbol Digit Modalities Test, Number Comparison, Stroop Color Naming, and Stroop Word Reading), working memory (Digit Span subtests forward and backward of the Wechsler Memory Scale-Revised and Digit Ordering), semantic memory (Verbal Fluency, Boston Naming, and the National Adult Reading Test), and episodic memory (Word List Memory, Word List Recall and Word List Recognition from the procedures established by the CERAD; immediate and delayed recall of Logical Memory Story A and the East Boston Story). The performances on 19 tests were converted to individual z scores using the mean and standard deviation of the baseline cognitive evaluation of the parent study sample. Averaging the z scores across all 19

measures of cognitive abilities produced a global cognitive function score as previously described (Wilson et al. 2003).

Neuroimaging—Magnetic resonance imaging (MRI) brain scans were completed on all study participants using a Siemens MRI scanner of 3T magnet strength (Waukesha, WI). A 3D magnetization-prepared rapid acquisition gradient-echo (MPRAGE) sequence was used to collect high-resolution T1-weighted anatomical data. Parameters of the MPRAGE scans were as follows: echo time (TE) = 2.98 ms, repetition time (TR) = 2.3 s, preparation time = 900 ms, flip-angle = 9°, field-of-view (FOV) = 25.6 cm × 25.6 cm, 176 sagittal slices, slice thickness = 1 mm, no gap, 256 × 256 acquisition matrix, parallel imaging acceleration factor of 2 along the phase encoding direction, for a total imaging time of 5 min and 30 s. A 2D fast spin-echo sequence was used to collect T2-weighted fluid attenuated inversion recovery (FLAIR) data. The FLAIR parameters were as follows: TE = 150 ms, TR = 9 s, inversion time = 2.49 s, FOV = 22 cm × 22 cm, 35 axial slices, slice thickness = 4 mm, no gap, 256 × 256 acquisition matrix, acceleration factor of 2, and a scan time of 2 min and 42 s. Finally, spin-echo echo-planar diffusion-weighted imaging data were collected according to the following parameters: TE = 85 ms, TR = 8.1 s, FOV = 22.4 cm × 22.4 cm, 65 axial slices, slice thickness = 2 mm, no gap, 112 × 112 acquisition matrix with 6/8 partial Fourier acceleration, $b = 1000 \text{ s/mm}^2$ for 40 diffusion directions uniformly distributed in 3D space, $b = 0 \text{ s/mm}^2$ volumes, for a total scan time of 6 min and 37 s.

Two DTI measures were utilized to characterize white matter structural integrity in the present study: fractional anisotropy (FA) and the trace of the diffusion tensor. Both have been associated with white matter integrity (Mukherjee et al. 2008), and are the two most commonly used measures derived from the diffusion tensor (Alexander et al. 2007). Correction of distortions in the diffusion-weighted volumes caused by eddy currents and magnetic field non-uniformities, bulk-motion correction, B-matrix reorientation, and generation of FA and trace maps were accomplished with TORTOISE (<http://www.tortoisedi.org>) (Pierpaoli et al. 2010; LeBihan et al. 2001; Basser and Pierpaoli 1996). White matter lesions appearing hyperintense in T2-weighted images and commonly referred to as white matter hyperintensities (WMHs) were segmented for each participant using a support vector machine classifier based on both MPRAGE and FLAIR information (WMLS, SBIA, University of Pennsylvania, PA) (Zacharaki et al. 2008), and a mask (0 and 1 s) was generated (voxels with WMH were given values of 1 in the mask). The WMH mask of each participant was transformed to the space of the corresponding processed DTI data based on the transformation of the FLAIR image volume to the pre-processed $b = 0 \text{ s/mm}^2$ volume. We have used the above processing approach in previous work (Han et al. 2016a, b).

Statistical analysis

The association of white matter diffusion measures with temporal discounting was analyzed using Tract-Based Spatial Statistics (TBSS; Smith et al. 2006). Individual FA volumes were spatially transformed in a non-linear manner to fit the IIT Human Brain Atlas (v.4.1) (<http://www.iit.edu/~mri>) mean FA template (Varentsova et al. 2014). The local FA maxima from each individual spatially transformed FA volume were then projected onto the IIT Human Brain Atlas (v.4.1) white matter skeleton. The same projection parameters were used to

project the trace and WMH mask values from the same voxels as the local FA maxima. Linear regression was then used to test the association of FA along the white matter skeleton (outcome) with temporal discounting (predictor), while adjusting for age, sex, level of education, the total volume of WMHs normalized by the intracranial volume, and the presence of WMHs at the voxel level. Analyses were then repeated further adjusting for cognitive function. Separate regression models were conducted to examine the association of the trace of the diffusion tensor along the white matter skeleton with temporal discounting, controlling for the same factors mentioned above. The null distribution was built using the “randomise” tool in FSL (FMRIB, University of Oxford, UK) and 5000 permutations of the data. Cluster differences were considered significant at $p < 0.05$, after correction using Family Wise Error (FWE). Clusters with significant effects were defined using the Threshold-Free Cluster Enhancement (TFCE) method (Smith and Nichols 2009). The IIT Human Brain Atlas (v.4.1) “regionstat” tool was used to determine a list of most probable connections passing through clusters showing significant effects, according to the information contained in the multi-layer, connectivity-based white matter labels of the IIT Human Brain Atlas (v.4.1) (developed using high angular resolution diffusion imaging probabilistic tractography).

Results

Descriptives

Descriptive data on all variables (demographic, cognitive, and temporal discounting) are reported in Table 1. The sample was predominantly female and white with an average level of education above high school. As would be expected of a non-demented sample of older adults, the average MMSE score was within the unimpaired range (mean MMSE = 28.29).

Temporal discounting association with white matter integrity—TBSS analysis demonstrated inverse correlations between the measure of FA and temporal discounting in multiple bilateral white matter regions throughout the brain, controlling for age, sex, years of education, and WMHs (see Fig. 1 and Supplementary Tables ST1 and ST2). Results revealed significant associations among connections between bilateral frontal regions, striatal–frontal regions, and temporal–parietal regions. Of all clusters that showed significance, clusters 1 and 2 of Fig. 1 in the prefrontal lobe and temporal lobe implicated connections between temporal and frontostriatal gray matter regions (Table 2).

TBSS revealed multiple direct associations between the trace of the diffusion tensor and temporal discounting throughout the brain, adjusting for the effects of age, sex, education, and WMHs (see Fig. 2 and Supplementary Tables ST3 and ST4). Again, results revealed significant associations among connections between bilateral frontal regions, striatal–frontal regions, and temporal–parietal regions. Again, of all clusters that showed significance, clusters 1 and 2 of Fig. 2 in the temporal lobe and frontal lobe implicated connections between temporal–parietal and frontostriatal gray matter regions. Results are shown in Fig. 2 and Table 3.

Analyses for FA were repeated after further adjusting for cognitive function. Significant inverse correlations were again observed bilaterally between FA values and temporal

discounting throughout the brain (see Fig. 3 and Supplementary Tables ST5 and ST6). Results revealed significant associations with connections between bilateral frontal regions, striatal–frontal regions, and temporal–parietal regions. Of all significant results observed, clusters 1 and 2 of Fig. 3 in the temporal lobe and prefrontal lobe implicated connections between temporal–parietal and frontostriatal gray matter regions. Results were almost identical to those identified from models that only adjusted for age, education, sex, and white matter hyperintensities, and are shown in Fig. 3 and Table 4.

Results for trace were further adjusted for cognitive function. Again, significant positive correlations were observed between trace and temporal discounting in bilateral white matter regions throughout the brain (see Fig. 4 and Supplementary Tables ST7 and ST8). Again, results revealed significant associations with connections between bilateral frontal regions, striatal–frontal regions, and temporal–parietal regions. Again, of all significant results observed in white matter regions, clusters 1 and 2 of Fig. 4 in the temporal and frontal lobe implicated connections between temporal–parietal and frontostriatal gray matter regions. Results were very similar to those identified from models that were only adjusted for age, education, sex, and white matter hyperintensities, and are shown in Fig. 4 and Table 5.

Discussion

In more than 300 older persons without dementia, we investigated the association of temporal discounting with well-accepted measures of white matter structural integrity using diffusion tensor imaging. Temporal discounting was associated inversely with FA and directly with trace after adjusting for important demographic variables and WMHs. These findings persisted after further adjusting for global cognitive ability. Specifically, multiple bilateral white matter regions throughout the brain were associated with temporal discounting. Many significant connections were observed between bilateral frontal regions, striatal–frontal regions, and temporal–parietal regions. Notably, significant associations were observed among connections between temporal–parietal and frontostriatal gray matter regions. These DTI results are consistent with our previously reported functional connectivity resting-state fMRI associations with temporal discounting in old age (Han et al. 2013), extend our work by broadly implicating white matter structural integrity as inversely associated with temporal discounting, and altogether suggest a link between temporal discounting and brain connectivity (structural and functional) in old age that is independent of global cognitive ability and demographic variables.

Our findings may be viewed as consistent with previous work investigating diffusion tensor imaging associations of temporal discounting in younger populations. In a group of 79 healthy participants ages 9 through 23, temporal discounting was observed to correlate with bilateral frontal and temporal white matter tract integrity measures (FA and mean diffusivity; Olson et al. 2008). This study controlled for the effects of age. Our study extends this work by investigating these associations in a much older cohort and further controlling for years of education, sex, and global cognitive function. In a study using a volume-of-interest approach focusing on frontostriatal white matter tract integrity, mean diffusivity and radial diffusivity were both associated with temporal discounting in a group of 40 healthy young adults ages 18 through 25 (Peper et al. 2013). Our trace results may be viewed as consistent

with this work as we also observed significant clusters in frontostriatal white matter. However, instead of taking a focused regional approach, we sought to investigate whole-brain associations of temporal discounting in older adults to determine the impact of other brain systems. Our results, therefore, extend this prior work by also highlighting the importance of temporal and parietal lobe white matter considerations.

One German-based study investigated functional and structural connectivity associations with a delay of gratification and a delay discounting paradigm in 40 healthy older adults (mean age = 74) using predefined 90-node and 12-node brain region networks (Hanggi et al. 2016). Functional and structural connections between nodes located in the frontostriatal regions were implicated after controlling for age, sex, intracranial volume, and head motion. With our current DTI results and that of our previous work with functional connectivity resting-state fMRI (Han et al. 2013), we too observed the importance of frontostriatal functional and structural connectivity networks in considering temporal discounting among older adults. Our work extends this work by also highlighting the importance of temporal and parietal lobe structural and functional connectivity associations of temporal discounting in older adults. Differences in results may be explained by differences in study approach. For example, our studies had higher numbers of participants (302 for the present DTI study and 123 for our previous fMRI study), and perhaps most importantly, we took a voxelwise whole-brain approach to our studies (as opposed to 90- or 12-region of interest approach restricted to the frontostriatal regions).

Overall, our white matter microstructure connectivity results are consistent with and extend our previous functional connectivity resting-state fMRI results (Han et al. 2013), and highlight the potential importance of connectivity between frontostriatal networks and temporal–parietal lobe networks when considering temporal discounting in old age. This is consistent with a model of temporal discounting previously discussed (Han et al. 2013, 2014, 2016) which posits that temporal–parietal lobe structures commonly implicated in memory abilities may serve important prospective imagery functions that facilitate representations of a “future self” with the greater reward option at a later time. These temporal–parietal lobe networks interact with frontostriatal networks involved in valuation processes, and this interaction may serve as a neurobiological mechanism for decision-making. Relevant to aging, medial temporal–parietal lobe structures and functions are known to be particularly susceptible to early age-related amyloid and tau neuropathological accumulation (Marks et al. 2017). Consequently, a neuroeconomic model of impaired decision-making in old age may be proposed whereby age-related neuropathology may accumulate and negatively impact temporal–parietal lobe networks ahead of noticeable functional or cognitive impairment. This “subclinical” neuropathological accumulation in temporal–parietal lobe networks may negatively impact prospective or “future-oriented” functions, thereby inhibiting the ability of these temporal–parietal lobe networks to interact with frontostriatal valuation networks, resulting in greater temporal discounting. More work is planned to investigate the components of this model and determine its relevance for changes in decision-making among older adults.

Limitations need to be acknowledged in the present study. First and perhaps foremost, the cross-sectional nature of these analyses clearly restricts our ability to make any causal

inferences on the direction of impact among the factors studied. Longitudinal studies could address this concern, and we will be able to examine this in the future. Temporal discounting may be considered a state or trait variable (Odom and Baumann 2010). The measure for the present study is likely sensitive to trait-like aspects of personality, consistent with the previous literature (Odom 2011). However, we are collecting this measure annually as it may also have state-like properties. Certain factors such as impulsivity and reward-seeking behavior could impact results, and our lack of addressing these is a limitation. Although TBSS is considered a strong statistical approach to investigate white matter integrity, it has been suggested that this approach may have some potential biases (Bach et al. 2014) and other limitations (Schwarz et al. 2014). For these reasons, other methods or approaches sensitive to white matter integrity might yield different findings. Finally, although DTI has been robustly used as a measure of white matter integrity, the underlying neurochemical and neurocellular mechanisms of these associations are still unclear. Animal model studies may assist to determine the underlying mechanisms of these associations.

Despite the noted limitations, our study has multiple strengths. These include a large sample of community-dwelling participants and the ability to empirically account for multiple variables that could impact white matter integrity findings, such as age, years of education, sex, white matter hyperintensities, and global cognition. Our findings suggest that temporal discounting is inversely associated with white matter integrity in old age even after considering demographic factors, white matter hyperintensities, and global cognitive ability. Longitudinal studies are needed to establish the causal direction of these factors. If declines in white matter microstructure integrity lead to greater temporal discounting, then cardiovascular and other interventions that have an impact on white matter integrity in old age (e.g., Voss et al. 2013; Marks et al. 2007) may also be useful for maintaining optimal decision-making in old age.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Fig. 1. Voxelwise results of fractional anisotropy (FA) negative association with temporal discounting in linear regression models adjusted for age, education, sex, the total volume of WMHs normalized by the intracranial volume, and the presence of WMHs at the voxel level. Each cluster has been numbered and a list of the connections with the most fibers through each cluster is provided in Table 2

Fig. 2.

Voxelwise results of trace positive association with temporal discounting in linear regression models adjusted for age, education, sex, the total volume of WMHs normalized by the intracranial volume, and the presence of WMHs at the voxel level. Each cluster has been numbered, and a list of the most probable connections passing through each cluster is provided in Table 3

Fig. 3. Voxelwise results of fractional anisotropy (FA) negative association with temporal discounting in linear regression models adjusted for age, education, sex, the total volume of WMHs normalized by the intracranial volume, the presence of WMHs at the voxel level, and cognitive function. Each cluster has been numbered, and a list of the most probable connections passing through each cluster is provided in Table 4

Fig. 4. Voxelwise results of trace positive association with temporal discounting in linear regression models adjusted for age, education, sex, the total volume of WMHs normalized by the intracranial volume, the presence of WMHs at the voxel level, and cognitive function. Each cluster has been numbered and a list of the most probable connections passing through each cluster is provided in Table 5

Table 1

Demographic and cognitive variables

Sample (<i>n</i> = 302)	
Age (years)	
Mean (SD)	81.38 (7.57)
Range	58.81–99.70
Education (years)	
Mean (SD)	15.75 (2.90)
Range	8–25
Sex (% female)	75.5% (<i>n</i> = 228)
Race (% white)	96.0% (<i>n</i> = 290)
MMSE (total score)	
Mean (SD)	28.29 (1.56)
Range	21–30
Global cognition <i>z</i> score	
Mean (SD)	0.35 (0.51)
Range	– 1.22 to 1.62
Temporal discounting	
Mean (SD)	0.0139 (0.0175)
Range	0.0026–0.0844

Table 2

List of the top eight most probable connections passing through white matter clusters 1 and 2 of Fig. 1 showing significant associations of fractional anisotropy (FA) with temporal discounting (models adjusted for age, education, sex, total volume of WMHs normalized by the intracranial volume, and presence of WMHs at the voxel level)

Cluster #	Significant voxels #	Connection between	Percent
1	704	R superior temporal	10
		R superior temporal	7
		R superior temporal	6
		R superior temporal	6
		R superior temporal	6
		R superior temporal	4
		R superior temporal	3
		R fusiform	3
2	1326	L superior frontal	16
		L superior frontal	10
		L superior frontal	9
		L superior frontal	6
		L superior frontal	6
		L superior frontal	5
		L superior frontal	4
		L superior frontal	3
		R inferior parietal	
		R lateral occipital	
		R hippocampus	
		R superior parietal	
		R pericalcarine	
		R fusiform	
		R banks of the superior tem-poral sulcus	
		R middle temporal	
		L rostral middle frontal	
		L medial orbitofrontal	
		R superior frontal	
		L putamen	
		L caudate	
		L parsopercularis	
		L thalamus-proper	
		R rostral middle frontal	

List derived from “regionstat” tool running on the IIT Human Brain Atlas (v4.1). The last column shows the probability that a fiber passing through a voxel of the cluster belongs to a certain connection. Cluster 1 had 23 possible connections and cluster 2 had 19 possible connections with a probability of at least 1%

Table 3

List of the top eight most probable connections passing through white matter clusters 1 and 2 of Fig. 2 showing significant associations of trace with temporal discounting (models adjusted for age, education, sex, total volume of WMHs normalized by the intracranial volume, and presence of WMHs at the voxel level)

Cluster #	Significant voxels #	Connection between	Percent
1	275	R hippocampus	R superior temporal 11
		R inferior temporal	R middle temporal 8
		R fusiform	R superior temporal 8
		R fusiform	R inferior temporal 8
		R fusiform	R middle temporal 6
		R hippocampus	R inferior temporal 4
		R middle temporal	R superior temporal 4
		R thalamus-proper	R superior temporal 4
2	1092	L caudate	L rostral middle frontal 9
		L putamen	L rostral middle frontal 9
		L putamen	L lateral orbitofrontal 4
		L thalamus-proper	L rostral middle frontal 4
		L insula	L rostral middle frontal 4
		L caudate	L lateral orbitofrontal 3
		R medial orbitofrontal	L medial orbitofrontal 3
		L caudate	L medial orbitofrontal 3

List derived from “regionstat” tool running on the IIT Human Brain Atlas (v.4.1). The last column shows the probability that a fiber passing through a voxel of the cluster belongs to a certain connection. Cluster 1 had 23 possible connections and cluster 2 had 17 possible connections with a probability of at least 1%

Table 4

List of the top eight most probable connections passing through white matter clusters 1 and 2 of Fig. 3 showing significant associations of fractional anisotropy (FA) with temporal discounting (models adjusted for age, education, sex, total volume of WMHs normalized by the intracranial volume, presence of WMHs at the voxel level, and global cognition)

Cluster #	Significant voxels #	Connection between	Percent
1	666	R superior temporal	10
		R superior temporal	6
		R superior temporal	6
		R superior temporal	6
		R superior temporal	6
		R superior temporal	5
		R superior temporal	3
		R fusiform	3
2	1264	L superior frontal	16
		L superior frontal	10
		L superior frontal	9
		L superior frontal	6
		L superior frontal	6
		L superior frontal	5
		L superior frontal	4
		L superior frontal	3
		L rostral middle frontal	3
		L medial orbitofrontal	10

List derived from “regionstat” tool running on the IIT Human Brain Atlas (v4.1). The last column shows the probability that a fiber passing through a voxel of the cluster belongs to a certain connection. Cluster 1 had 24 possible connections and cluster 2 had 19 possible connections with a probability of at least 1%

Table 5

List of the top eight most probable connections passing through white matter clusters 1 and 2 of Fig. 4 showing significant associations of trace with temporal discounting (models adjusted for age, education, sex, total volume of WMHs normalized by the intracranial volume, presence of WMHs at the voxel level, and global cognition)

Cluster #	Significant voxels #	Connection between	Percent
1	86	R inferior temporal	R middle temporal
		R fusiform	R inferior temporal
		R fusiform	R middle temporal
		R fusiform	R superior temporal
		R middle temporal	R superior temporal
		R hippocampus	R superior temporal
		R amygdala	R middle temporal
		R inferior temporal	R lateral occipital
2	2230	L parsopercularis	L superior frontal
		L caudate	L rostral middle frontal
		L putamen	L rostral middle frontal
		L supramarginal	L rostral middle frontal
		L caudal middle frontal	L parsopercularis
		L thalamus-proper	L superior frontal
		L middle temporal	L rostral middle frontal
		L inferior parietal	L rostral middle frontal

List derived from “regionstat” tool running on the IIT Human Brain Atlas (v4.1). The last column shows the probability that a fiber passing through a voxel of the cluster belongs to a certain connection. Cluster 1 had 20 possible connections and cluster 2 had 27 possible connections with a probability of at least 1%