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Diffusion connectometry reveals white matter substrates of individual differences in loss aversion

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While neural responses in striatal, limbic and somatosensory regions are known to track individual differences in *loss aversion*, a system-level view of its neural basis is still lacking, and, in particular, a possible association with white matter (WM) microstructural organization remains unexplored. We investigated the relationship between behavioural loss aversion and fractional anisotropy (FA), a popular diffusion tensor imaging (DTI) metric of WM coherence, in 130 healthy young participants. Loss aversion was positively correlated with FA in bundles that might underpin attentional biases towards negative stimuli (forceps minor), the associated aversive affective states (fornix), and the motivational incentive to avoid them (cingulum). Conversely, a negative correlation was found in bundles previously associated with reward sensitivity through projections to fronto-striatal structures (superior longitudinal fasciculus and inferior fronto-occipital fasciculus), possibly decreasing loss aversion by enhancing the salience of potential gains. The observation of positive *and* negative correlations with FA in distinct WM bundles supports the view that loss aversion reflects the interplay between oppositely-directed reward- and loss-oriented patterns of brain activity and connectivity. These results strengthen the view that loss aversion represents a stable neuro-cognitive component of one's behavioural attitude in risky decision-making, rather than a transient fearful reaction to choice-related information.

Keywords Loss aversion, Diffusion tensor imaging, Fractional anisotropy, Risky decision-making, Intervention, Brain connectivity

Against economic prescriptions based on so-called "expected value"[1], which weigh the positive and negative consequences of choices equally, individuals are typically more inclined to avoid losses than acquire gains[2]. This behavioural asymmetry is considered to reflect a cognitive mechanism of "*loss aversion*" (LA), i.e., weighing prospective losses more than equivalent gains in decision-making under risk[2]. Individual differences in LA are usually investigated with series of *mixed gambles* offering equal (50%) probability of either gaining or losing different amounts of money[3–5], and measured in terms of a λ coefficient representing the multiplicative weight assigned to losses compared with gains[4,6]. This well-established approach highlighted an average λ around 2 in healthy participants[6–8], with a minority of loss-neutral (λ ≈ 1) individuals[6,9].

Likely due to its relationship with critical drivers of behavioural control such as interoception (i.e., "*feeling one's own body*"[10]), and emotion regulation[11], LA is considered to shape not only economic decisions (e.g., financial market[12]) but virtually any kind of evaluation (e.g., organ donation[13], brand choice[14], food choice[15]). Unveiling the neuro-cognitive precursors of individual differences in LA might therefore enable a better understanding of human nature[4], which explains why many efforts have been made to investigate its neurobiological correlates.

Crucial evidence, in this respect, has been provided by neuroimaging studies addressing the relationship between LA and metrics of brain function and/or structure, and interpreted with the lens of *Neuroeconomics*[16]. In this framework, decision-making is considered to reflect the interplay between *appetitive drives* generated

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by frontomedial-striatal structures and *aversive drives* involving limbic and somatosensory structures, favoring approach and avoidance behaviour, respectively[17]. These appetitive and aversive neural systems are generally activated by prospective gains and losses, respectively[18]. Neuroimaging studies have shown, however, that some of their components underpin oppositely-directed patterns of "*neural loss aversion*" (NLA), i.e., a bidirectional response in which the asymmetry between loss- and gain-related components reflects individual differences in behavioural LA ([9,19] for an overview see[4]). Such pattern has been found in the posterior insula and amygdala (more activated by anticipated losses than deactivated by gains ([9,16]; i.e., "loss-oriented NLA"), as well as in the ventral striatum and midcingulate cortex (more deactivated by anticipated losses than activated by gains ([9,19,20]; i.e., "gain-oriented NLA"). In the midcingulate cortex, the presence of both gain- and loss-related neural signals might then support cost-benefit analyses[4,21], as well as behavioural adjustments in conjunction with the dorsolateral prefrontal cortex (dlPFC[22]).

This view of the neural basis of LA is supported by distinct studies, showing a relationship between its behavioural expression and the responsiveness of both amygdala[11,20,23] and insula[24,25], as well as grey matter (GM) volume in amygdala, striatum, insula and thalamus[9,26]. The involvement of the amygdala is also supported by lesional evidence[27]. Other results however suggest that these brain structures might play a more complex role in LA, thus raising the need for further inquiry[4]. First, against some of the aforementioned findings, a negative correlation has been reported between LA and GM volume in the posterior insula[28], and suggested to reflect anomalous salience detection and loss processing, in turn biasing choices towards loss avoidance. Moreover, the activity of the amygdala was found to track the *deviation* of the gain-loss ratio from the individual decision boundary (λ), which suggests that it might encode a "subjective value" integrating appetitive and aversive signals rather than these single components alone[29]. Finally, against its involvement in coding prospective and actual gains[30], the striatum was found deactivated by the presence of possible high performance-dependent gains, that might be coded as negative stimuli because they emphasize the adverse consequences of failure[31]. Overall, these findings might appear to cast doubts on the view of LA as emerging from the interplay between gain- and loss-oriented patterns of neural loss aversion involving frontomedial-striatal and limbic-somatosensory structures, respectively.

We tackled this issue by investigating - for the first time - the possible association between LA and fractional anisotropy (FA), a popular metric of white matter (WM) organization estimated through diffusion tensor imaging (DTI). To date, DTI has been only used to investigate a relationship between FA and individual differences in other facets of decision-making, such as impulsivity[32–34], temporal discounting[35,36], reward-based learning[37], and risk-seeking on the Balloon Analogue Risk Task (BART)[38,39]. In particular, the integrity of connections between midbrain and striatum was positively correlated with total earnings on the BART[39], while those between insula and striatum were additionally associated with the overall number of risky choices. These data suggest that adaptive decision-making requires a balance between neural signals tracking (a) the size of a potential reward, and (b) value integration and risk representation, conveyed by tracts connecting the striatum with, respectively, midbrain and insula[39]. The lack of previous DTI studies on LA is surprising not only because this level of evidence might provide novel insights into a controversial literature, but also because of the well-established relationship between such metrics and task performance[40,41], contributing to unveil the neural bases of cognitive processes both in healthy[42,43] and clinical[44,45] populations.

On these grounds, we investigated a relationship between behavioural LA and WM-FA in a large sample of 130 healthy young participants. Exploratory analyses were also performed, by modeling additional DTI metrics such as axial diffusivity (AD), mean diffusivity (MD), and radial diffusivity (RD). Based on the available related evidence[39,46], we first predicted that this association would involve bundles connecting insula, striatum, and the prefrontal cortex (PFC). In particular, based on the hypothesis that LA reflects the interplay between gain- and loss-oriented patterns of neural loss aversion[9], we predicted that it would correlate positively and negatively with FA in WM bundles involving limbic-somatosensory and frontomedial-striatal structures, respectively.

Materials and methods

Participants

We collected behavioural and DTI data from 130 right-handed healthy volunteers (70 females and 60 males; mean age = 24.43 years, standard deviation (SD) = 3.32, range = 18–40). None of the participants had a history of substance abuse or neuropsychiatric diseases, nor reported to be on a medication that might interfere with cognitive functions. They gave their written informed consent to the experimental procedure, that was approved by the local Ethics Committee and performed in accordance with the Declaration of Helsinki.

Behavioural data collection

Participants' choices in a series of mixed-gambles allowed to estimate their degree of LA, under the assumption that the latter must be isolated from risk attitude (i.e., sensitivity to outcome variance) because both are involved in anticipatory evaluation processes[10]. To this purpose, before the Magnetic Resonance Imaging (MRI) session, they participated in two behavioural tasks, that were presented in counterbalanced order with random shuffling of trial order. In one task they were presented with a series of 49 mixed (i.e., "gain-loss") gambles requiring choosing between the status quo (i.e., 0) and a gamble that might result in equally probable (50% probability) gain or loss. The gain-loss values, sampled from a 7 × 7 matrix, were centered to a λ level of 2, which is representative of the general population[2,7,8]. The second task included 30 "gain-only" gambles requiring choosing between a certain (100% probability) gain outcome and 50% chances of a larger gain (or 0).

Prior to participation, they received detailed instructions and completed a training session to familiarize with task requirements. Moreover, they were provided with a monetary incentive, and asked to place it in their wallet[3,11,47]. They were then informed that this sum would increase or decrease according to their actual

performance in the tasks, with their final payoff depending on the outcome of one gain-loss trial and one gain-only trial randomly drawn from those played.

MRI data acquisition

We collected Diffusion Weighted Imaging (DWI) MRI data with a General Electrics (GE) Discovery MR750 3-Tesla scanner (GE Healthcare), equipped with a 16-channels head coil. Participants were positioned on the scanner bed, and both foam pads and earplugs were used to make the acquisition more comfortable, and to minimize head movements. A DTI diffusion scheme was used, and 81 diffusion sampling directions were acquired with b-value = 1000 s/mm^2, in-plane resolution = 1 × 1 mm^2, and slice thickness = 2 mm, plus 2 non-DWI (b0) images.

LA Estimation

The individual LA level was estimated from each participant's choices, under the assumption that both gain-loss and gain-only trials are necessary to separate loss aversion from risk aversion[10]. In keeping with models derived from Prospect Theory[2], the probability of accepting a gamble can be estimated as follows:

$$(accept\ gamble|G,L,B) = \frac{1}{1+e^{-\mu\ \times\ (p_G\times(G)\ ^{\rho}-\lambda\times p_L\times(-L)^{\rho}-B^{\rho})}}$$

where G is the gain (G > 0), L is the loss (L < 0 for gain-loss trials and L = 0 for gain-only trials), B is the guaranteed gain (B = 0 for gain-loss trials and B > 0 for gain-only trials), p_G=0.5 is the probability of a gain and p_L=1- p_G =0.5 is the probability of a loss. The free parameters of the model are: (a) the LA lambda (λ), i.e., the multiplicative weight associated with anticipated losses compared with gains; (b) the risk attitude rho (ρ), i.e., the curvature of the value function $u(x) = x^{\rho}$ that embodies the diminishing sensitivity to increasing outcome; and (c) the choice consistency or "softmax temperature" (μ), i.e., a measure of noisiness vs. systematicity in choices. These parameters were individually computed via maximum likelihood estimation with MATLAB (MathWorks, Natick, MA).

Pre-processing and connectometry analysis of MRI-DTI data

We used DSI Studio ("Chen" release; http://dsi-studio.labsolver.org) both for the pre-processing and the connectometry analysis of MRI-DWI data. The "FSL eddy" tool was used to correct for eddy current distortions, through the integrated interface in DSI Studio. Imaging data underwent both visual and automatic quality control steps, with raw diffusion data being checked for major movements, or "bad slices" with artifacts, both before and after the FSL eddy correction. Neighboring DWI correlation was used as an indicator of the final quality of diffusion data, with minimum and average values of 0.79 and 0.85, respectively. The accuracy of b-table orientation was examined and adjusted by comparing fiber orientations with those reported in a population-averaged template[48].

MRI connectometry is grounded in the concept of local connectome, i.e., "*the degree of connectivity between adjacent voxels within a white matter fascicle, quantified by the density of diffusing spins*"[49]. The individual diffusion MRI datasets were reconstructed in the Montreal Neurological Institute (MNI) space using q-space diffeomorphic reconstruction[50], with a diffusion sampling length ratio of 1.25, through restricted diffusion imaging[51]. DSI Studio employs different algorithms for the computation of tensor-derived metrics, depending on the acquisition protocol. Since single-shell images with a b-value of 1000 s/mm² were collected, we applied the diffusion tensor model recommended for datasets with b-values below 1750 s/mm^2, and data were resampled to 2 mm isotropic. For each voxel, diffusion tensors are computed and sampled along predefined WM fiber directions derived from a standard atlas. This sampling procedure results in quantitative measures of local connectome integrity, reflecting the degree of connectivity between adjacent voxels along specific fiber pathways. For each subject, the resulting local connectome measures are arranged into a one-dimensional vector. These individual vectors are then concatenated across all participants to form a two-dimensional matrix of size m × n, with m representing the number of local connectome features per subject, and n the total number of participants, respectively. This matrix is subsequently modeled in statistical analyses to assess the relationship between local connectome features and the behavioral variable(s) of interest.

Here we used Diffusion MRI connectometry[52] to generate the correlational tractography based on the requirement of a non-parametric Spearman correlation between individual voxel-wise FA and λ (i.e., LA) values. To this purpose, we used a deterministic fiber tracking algorithm[53] with a seeding region placed at the whole brain, while the cerebellum was excluded from tracking. To isolate the bundles in which FA values were significantly correlated with behavioural LA we used a p< 0.05 threshold, corrected for multiple comparisons with False-Discovery-Rate (FDR[54]), and a minimum of 10 tracts. The FDR was estimated with a nonparametric, permutation-based, testing procedure. Namely, the connectome matrix underwent 4000 random permutations generating an equal number of "null" local connectome matrices. For each permuted matrix, an automated fiber tracking algorithm was used to reconstruct pathways showing considerable associations with LA (T > 2.5). The lengths of the resulting tracts on each permutation were recorded to generate a null distribution of tract lengths. This was then compared to the distribution obtained from the actual (non-permuted) data, thereby allowing to assess whether the observed tract-level associations exceeded what would be expected by chance. The tracts that were positively or negatively correlated with behavioural LA at p < 0.05 FDR corrected were then clustered through the DSI "Recognize and cluster" function. The same connectometry pipeline was also used in a control analysis modeling sex as covariate, to assess its possible effect on FA results.

Importantly, although advanced diffusion models such as "Neurite Orientation Dispersion and Density Imaging" (NODDI[55]) or "Diffusion Kurtosis Imaging" (DKI[56]) can provide additional microstructural insights,

we used DTI for its robustness, widespread validation, and compatibility with our dataset in terms of b-value and number of directions. Moreover, FA has been previously related to behavioral decision-making attitudes (e.g.,[57]) - thus enabling a comparison with available evidence - and provides a reliable proxy of WM integrity. Since the latter can be assessed via further DTI metrics of WM microstructure, we performed exploratory analyses of mean diffusivity (MD, tracking global tissue density) as well as axial and radial diffusivity (AD and RD, tracking tissue coherence and myelination), respectively.

Results

Behavioral results

LA data were not normally distributed (Kolmogorov-Smirnov d = 0.192, Shapiro-Wilk: W = 0.71143, $p < 0.0001$). In keeping with a well-established literature[8], the mean and median of behavioural LA were 2.109 and 1.946 (interquartile range (IQR) = 0.609), respectively, with no significant difference between males and females (Mann-Whitney U = 1943, $p = 0.466$). The mean LA degree of our sample was significantly higher than the "loss-indifference" $\lambda = 1$ ($p < 0.0001$) but not significantly different from $\lambda = 2$ ($p = 0.334$), which confirms the tendency to weigh potential losses about twice as much as potential gains in decision-making under risk.

DTI results

Figure 1 depicts the WM bundles showing a significant relationship between whole-brain FA values and behavioural LA in connectometry analyses. We found a *positive correlation* between LA and FA in the fornix, cingulum and forceps minor (i.e., the anterior part of corpus callosum) bilaterally (Fig. 1-top). Conversely, a *negative correlation* with LA was observed in the bilateral dorsal part of the superior longitudinal fasciculus and left inferior longitudinal fasciculus (SLF and ILF), as well as in the bilateral inferior fronto-occipital fasciculus (IFOF), bilateral parahippocampal cingulum, right frontal aslant tract (FAT) and right forceps major (i.e., the posterior part of corpus callosum) (Fig. 1-bottom). Correlation values ranged from 0.22 to 0.26 (Table 1), indicating a small effect-size. In keeping with the lack of a significant effect of sex on LA, these results were confirmed when including this variable as covariate (Supplementary Fig. 1).

Exploratory analyses on other DTI metrics unveiled a positive correlation between behavioural LA and AD in the right cingulum, while a negative correlation was detected in the bundles spreading bilaterally towards the forceps major and the tapetum of the corpus callosum (Supplementary Fig. 2A-B). The latter negative relationship was also found with MD and RD, that instead displayed no significant positive correlation with LA (Supplementary Fig. 2C-D).

Discussion

The neural correlates of LA have been extensively investigated both in terms of brain response with *f*MRI[4,6], and of underlying GM properties with voxel-based-morphometry (VBM[26]). Instead, a possible relationship with structural connectivity, and particularly WM microstructural organization, remains unexplored. We aimed both to fill this gap, and to inform a partially inconsistent literature on the roots of LA in the neural mechanisms shaping approach and avoidance behaviours. To this purpose, we investigated a possible relationship between behavioural LA and *fractional anisotropy* (FA), a popular DTI metric of WM organization, in a large sample of 130 healthy young participants. In particular, we aimed to provide novel insights into the hypothesis that individual differences in LA reflect the interplay between oppositely-directed mechanisms of neural loss aversion involving fronto-striatal vs. limbic-somatosensory structures[4,9]. In line with this view, we found both positive and negative correlations between behavioural LA and FA in bundles connecting distinct brain networks.

As expected, we observed a *positive correlation* between LA and FA in WM bundles connecting key nodes of limbic-somatosensory networks, such as the fornix, cingulum and forceps minor. The available evidence on the connectivity patterns of these bundles, and the resulting cues about some of their possible functional roles, help refine the picture of LA as emerging from the interplay between brain networks promoting punishment vs. reward sensitivity. The *fornix* connects the hippocampus to different subcortical nodes of the limbic system, such as the septal nuclei, mammillary bodies, and hypothalamus[58]. It is considered to convey interoceptive signals, thereby supporting different facets of emotional and motivational learning such as fear conditioning, reversal learning, as well as episodic and non-declarative memory[59]. While animal studies show that fornix lesions impair freezing in fear conditioning (particularly involving the encoding and retrieval of contextual memory[60]), evidence from human participants suggests that this projection tract plays a key role in fear and anxiety[61], which might explain why its alterations reflect in affective dysregulation[62]. Also the *cingulum* is a key component of the limbic-emotional system[63], originating in the medial temporal lobe (amygdala and parahippocampal gyrus[64]) and encircling the corpus callosum up to the subgenual cortex[65–67]. On their way, cingulum fibers receive projections from regional "U-shaped" association fibers interconnecting the temporal, occipital, parietal, and frontal lobes, likely interfacing their neural signals and thereby supporting complex functions at the crossroad of affective, executive and motivational domains[68,69]. While this complex neural circuitry accounts for the multifaceted functional role of the cingulum[68], LA was specifically related to FA of its anterior sector, previously associated with decision-making and its modulation by affective cues[63]. Observing this relationship also for AD suggests that behavioral LA is also modulated by tissue coherence, alongside microstructural integrity tracked by FA, in the cingulum. Finally, the *forceps minor*, also known as the anterior forceps, connects the medial and lateral PFC bilaterally[70], crossing the midline via the genu of the corpus callosum[71,72], and is considered to underpin emotion regulation and attention control skills[73]. Interestingly, the FA of the forceps minor has been found correlated with the severity of symptoms of obsessive-compulsive disorder (OCD)[74], which might reflect its role in biasing information processing towards negatively-valenced affects, cognitions

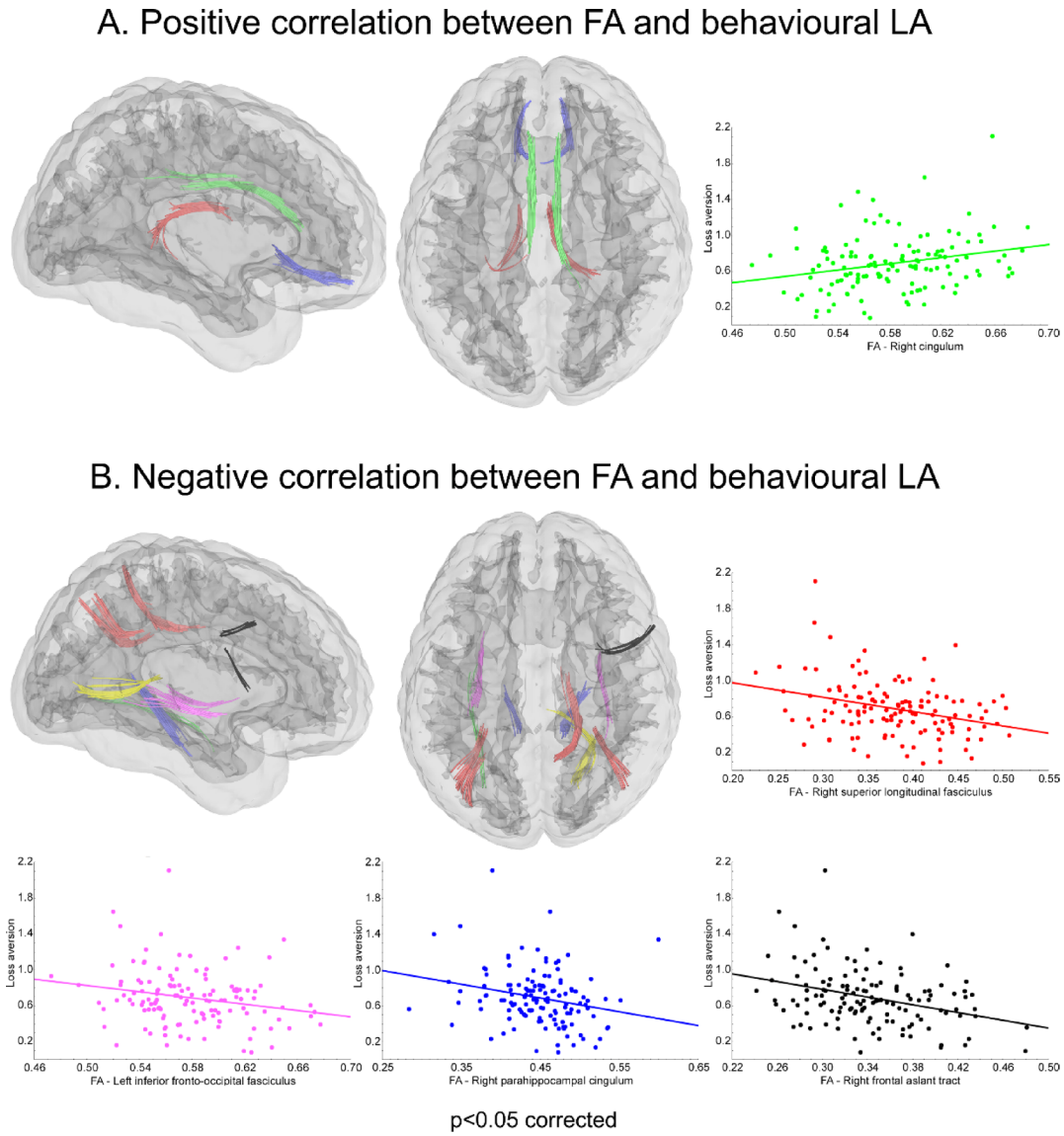

Fig. 1. The top figure sector depicts 3D tractograms of WM bundles showing a positive correlation between behavioural LA and FA in connectometry analyses, i.e., fornix (red), cingulum (green), and forceps minor (blue). The bottom figure sector shows the bundles in which FA is negatively correlated with behavioural LA, i.e., superior longitudinal fasciculus (red), left inferior longitudinal fasciculus (green), parahippocampal cingulum (blue), inferior fronto-occipital fasciculus (magenta), alongside right forceps major (yellow) and right frontal aslant tract (black). Scatterplots depict the relationship between FA and LA for selected representative tracts represented by the same color. Statistics were thresholded at $p < 0.05$, corrected for multiple comparisons with False Discovery Rate, with minimum number of 10 tracts. Following[10,11], LA was recalculated as its natural logarithm prior to display.

and/or motivations[75]. This hypothesis is also supported by studies on rats injected with quinpirole, an agonist of dopamine D2/D3 receptors eliciting OCD-like symptoms[76]. Compared with control rats, indeed, these animals displayed compulsive/checking behavior, associated with larger FA values in the forceps minor ([77] but see[78] for different results, and[79] for an overview). The involvement of these WM bundles in LA should be interpreted in the light of the direct relationship between higher FA values and more efficient neural signaling (i.e., faster and more reliable information transfer along axons[80]), as confirmed by the well-established FA decrease in a variety of pathological conditions such as Alzheimer disease[81], Parkinson's disease[82], or frontotemporal dementia[83]. Under this assumption, the positive correlation with FA in the forceps minor, fornix and cingulum might reflect the contribution of these bundles to the different cognitive-attentional, affective and motivational facets of LA, enhancing, respectively, the attentional salience of losses over gains, the associated negative affective states, and, accordingly, the motivational incentive for loss/risk avoidance. By supporting the attentional and affective processing of valenced stimuli[84] through fronto-limbic connnections, these bundles might drive the overweighing of negative ones that is inherent in the notion of LA. The bilateral engagement of evolutionarily

H	White matter bundle	T-score	Effect-size
Positive correlation with LA			
Left	Fornix	2.5	0.22
Right	Fornix	2.8	0.24
Left	Cingulum	2.7	0.23
Right	Cingulum	2.9	0.25
Left	Forceps minor	2.6	0.22
Right	Forceps minor	2.7	0.23
Negative correlation with LA			
Left	Superior longitudinal fasciculus 1	2.6	0.22
Right	Superior longitudinal fasciculus 1	3.1	0.26
Right	Superior longitudinal fasciculus 2	2.7	0.23
Left	Inferior longitudinal fasciculus	2.5	0.22
Left	Inferior fronto-occipital fasciculus	2.6	0.22
Right	Inferior fronto-occipital fasciculus	2.5	0.22
Left	Parahippocampal cingulum	2.7	0.23
Right	Parahippocampal cingulum	2.7	0.23
Right	Frontal Aslant Tract	2.6	0.22
Right	Forceps major	2.7	0.23

Table 1. The table reports the statistical value and effect-size (correlation coefficient) of the relationship between behavioural LA and FA in the bundles surviving a $p < 0.05$ FDR corrected statistical threshold with a minimum of 10 tracts.

ancient structures, such as the limbic regions, in supporting LA may reflect a deeply rooted neural mechanism for avoiding harm and negative outcomes, potentially accounting for the widespread and cross-species persistence of this bias across cultures and developmental stages[6].

The fact that FA in other WM tracts was negatively correlated with behavioural LA fits with the existence of an oppositely-directed neural circuitry, promoting reward seeking even more than loss avoidance. Such a relationship was found in the superior longitudinal fasciculus (SLF) and inferior fronto-occipital fasciculus (IFOF) bilaterally, alongside the left inferior longitudinal fasciculus (ILF) - all conveying signals from caudal to rostral prefrontal areas - as well as in the parahippocampal cingulum bilaterally alongside right forceps major and frontal aslant tract. Concerning the *SLF*, among its three branches connecting frontal and parietal areas[85], we found a positive correlation with LA in its dorsal component (i.e., SLF I), which connects the superior parietal and superior frontal cortex (particularly projecting to dorsal premotor and dorsolateral prefrontal regions)[86]. While SLF I is generally considered to support the voluntary orientation of visuospatial attention and motor control[85], in the case of decision-making a positive correlation was previously found between FA in the SLF and reward sensitivity[87]. This finding fits both with the notion that the efficiency of this circuitry is inversely related to punishment sensitivity and its behavioral outcomes such as loss/risk avoidance, and with evidence of decreased FA, in the SLF, in a clinical condition characterized by decreased reward seeking[88] such as depression[89]. Also in the case of the *IFOF*, a negative correlation between FA and LA might be interpreted in terms of its role in enhancing the salience of rewards[90]. This ventral tract connects the inferior and medial occipital cortex (lingual gyrus and cuneus) to the medial and lateral sectors of the orbitofrontal cortex[91], that are known to represent multiple facets of reward value by integrating positively- and negatively-valenced signals[92,93]. Some fibers of this tract project also to the striatum, thus establishing a cortico-striatal connection[94] that is known to support reward sensitivity[95,96]. The close relationship between the structural properties of this bundle and the functional responsiveness of its target structures has been previously confirmed by a positive correlation between FA in the IFOF and reward-related activation in the ventral striatum[90,97]. Alongside these data, our evidence of a negative correlation between LA and FA in the IFOF suggests that - similarly to the SLF - this bundle conveys neural signals enhancing the salience of expected rewards even more than possible losses.

Importantly, observing opposite correlation patterns between LA and FA in different WM tracts not only fits with the presence of both gain- and loss-oriented "neural loss aversion" drives[9,19], but additionally highlights the need of further mechanisms in charge of conflict monitoring and resolution. This requirement might explain the involvement of the right frontal aslant - connecting the caudal portion of the superior frontal gyrus (SFG) with the ventral premotor cortex and the caudal inferior frontal gyrus[98] - that has been previously associated with inhibitory control and conflict monitoring for action[99]. In line with the lateralization of our findings, this bundle is considered to convey neural information supporting conflict resolution and choice selection, particularly in the right hemisphere[100], as well as predictive over reactive strategies[101]. Conflict resolution might be also supported by the *forceps major*[102], connecting the occipital lobes through the splenium of the corpus callosum[103], in which a negative relationship with behavioural LA was also found for AD, MD and RD, in addition to FA. This bundle is primarily considered to mediate a general-purpose function such as the integration of visual information[104], which helps interpreting its role in key processes for conflict resolution such as executive functioning and working-memory[105]. Interestingly, FA of both the SLF and the forceps major have been associated with high

impulsivity in healthy participants performing a Delay Discounting task, thus supporting the view that both bundles are involved in reward seeking[32].

There are limitations to this study. First, although using corrected statistical thresholds is expected to ensure robust findings, the observed associations between DTI metrics and LA were generally weak, and could be detected only through a tract-wise correction approach. This is not surprising, however, as other explanatory levels such as functional connectivity might be expected to shape LA even more than WM features, which highlights the importance of addressing this relationship with a multimodal approach merging distinct (f) MRI features. The strength of findings might also reflect some methodological limitations. On one hand, while DTI provides meaningful indices of WM microstructure such as FA, future studies may further unveil the neurobiological bases of LA via more advanced models such as NODDI or DKI54,55. Moreover, the lack of an explicit correction of susceptibility artifacts during preprocessing may have affected the spatial accuracy of our findings, particularly in frontal and anterior temporal WM bundles. However, several prior studies have reported significant associations between DWI-DTI metrics and cognitive-behavioral measures even without such correction, and our relatively large sample is expected to enhance the robustness of the observed effects. Finally, interpreting some of the observed negative correlations is not straightforward, in the light of the available literature. On one hand, the interpretation of the IFOF role in LA remains controversial, as the opposite evidence of a negative correlation between reward sensitivity and WM integrity in this tract has been also reported[87]. One possible account of such inconsistency is that the latter study focused on fun-seeking, thus measuring sensitivity to signals of reward or non-punishment while neglecting the evaluation of truly negative events such as losses, and, therefore, of LA. Another unexpected finding is the negative correlation between LA and FA value in the inferior longitudinal fasciculus (ILF), a ventral tract connecting the occipital cortex to key nodes of the anterior and medial temporal lobe[106] such as amygdala and hippocampus[107]. This fasciculus has been associated with social and spatial perception, and with semantic processing[108]. Cues into its possible role in LA come from clinical studies, reporting reduced FA of this bundle in individuals with social anxiety disorder[109], which might reflect the bias towards negative information characterizing this condition[110]. Moreover, alterations of the ILF have been associated with impulsivity in adolescents with a family history of dependence[111]. In the light of these previous findings, the present evidence suggests that the ILF might contribute to the modulation of decision-making by affectively-valenced signals, and therefore to individual differences in the sensitivity to prospective losses vs. gains. Moreover, in line with evidence of stronger left-lateralized ILF connectivity supporting semantic, spatial, and emotional processing[108], our findings indicate that only the left tract was implicated in LA. Finally, while behavioural LA was positively correlated with FA in the anterior part of the cingulum, the opposite pattern was found in its posterior part, i.e., the parahippocampal cingulum. The available evidence from patients with memory deficits suggest that this bundle might play a role in memory functions[112], but whether this holds in normal conditions remains debated[62]. Therefore, although memory processes might support decision-making[113–117], further evidence is required to clarify the role played by this bundle in LA.

In conclusion, we report the first evidence linking WM microstructure to individual differences in LA in healthy young adults, providing novel insights across multiple levels of analysis. Observing both positive and negative correlations between LA and FA in distinct WM bundles support the presence of two oppositely-directed – i.e., loss-oriented and gain-oriented - neurocognitive patterns underlying LA. The former appears to enhance LA via greater WM microstructural coherence in bundles that might underpin attentional biases towards negative stimuli (forceps minor), the associated aversive affective states (fornix), and the motivational incentive to avoid them (cingulum). In contrast, the gain-oriented pattern, which may attenuate LA, involves bundles previously associated with reward sensitivity through projections to fronto-striatal structures (superior longitudinal fasciculus and inferior fronto-occipital fasciculus), possibly decreasing loss aversion by enhancing the salience of potential gains.

These findings were largely supported by the analysis on AD, albeit involving less extensive networks, which fits with the association between the degree of axonal coherence captures by this parameter[118] and WM organization as coded by FA in healthy individuals[119]. Instead, the general lack of significant findings for MD and RD warrants further investigation, through targeted studies, to clarify whether these indices can meaningfully reflect the relationship between cognitive processes and structural connectivity in healthy individuals, or whether they are more suitable as clinical markers of myelination (RD) and global tissue density (MD)[120].

These findings contribute to a longstanding debate on the nature of LA. On one hand, observing that individual differences in its behavioural expression also reflect the responsiveness of brain structures involved in affective and interoceptive processing (see[121] for a recent meta-analysis) might be considered to suggest that this "*cautionary brake on behaviour*"[27] constitutes a transient fearful overreaction elicited by choice-related information, rather than a stable component of one's preference function[122]. This hypothesis is weakened, however, by at least two sources of evidence. First, the fact that the relationship between behavioural and neural loss aversion holds even in resting-state brain activity, in the same striatal and insular regions previously found active when making choices during *f*MRI scanning[46]. Second, neurostructural evidence shows that individual differences in LA are correlated with GM volume in structures involved in somatosensory and affective processing such as insula[26,123], alongside amygdala and striatum[9,124,125]. The present evidence on WM organization complements these previous findings, thereby strengthening the view that LA represents a stable neuro-cognitive component of one's behavioural attitude in decision-making under risk.

The implications of this hypothesis are clearly shown by the ubiquity of LA, that has been reported regardless of one's professional group (e.g., expert traders[126] or taxi drivers[127]) and age (i.e., in adolescent, adult and elderly individuals[128,129]), and even in non-human species such as capuchin monkeys[130]. Observing a neuro-structural basis of LA fits with its stability over time, in turn making its degree a reliable measure of an individual's decision-making and behavioural attitude[6]. This is even more relevant if one considers that LA is negatively associated with psychological well-being[131], which might relate to the abnormal LA degree reported in several clinical

conditions such as alexithymia[132], depression with suicide attempts[133], schizophrenia[134–136] and substance addiction[137]. Therefore, unveiling the neurobiological bases of LA is important not only to gain insights into the processes underlying decision-making under risk, but also to delve into its impact in clinical populations[138], and to envision innovative treatments aimed at improving patients' quality of life, such as neurostimulation protocols targeting its key neural correlates[139,140].

Data availability

The datasets generated during the current study are available from the corresponding author on reasonable request.

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Declarations

Competing interests

The authors declare no competing interests.

Additional information

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