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Association between white matter microstructural changes and aggressiveness. A case-control diffusion tensor imaging study

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ABSTRACT

Research has focused on identifying neurobiological risk factors associated with aggressive behavior in order to improve prevention and treatment efforts. This study aimed to characterize microstructural differences in white matter (WM) integrity in individuals prone to aggression. We hypothesized that altered cerebral WM microstructure may underlie normal individual variability in aggression and tested this using a case-control design in healthy individuals. Diffusion tensor imaging (DTI) was used to examine WM changes in martial artists (n = 29) and age-matched controls (n = 31). We performed tract-based spatial statistics (TBSS) to identify differences in axial diffusivity (AD), fractional anisotropy (FA) and mean diffusivity (MD) between the two groups at the whole-brain level. Martial artists were significantly more aggressive than controls, with increased MD in parietal and occipital areas and increased AD in widespread fiber tracts in the frontal, parietal and temporal areas. Positive associations between AD/MD and (physical) appetitive aggression were identified in several clusters, including the corpus callosum, the superior longitudinal fasciculus and the corona radiata. Our study found evidence for WM microstructural changes associated with aggressiveness in a community case-control sample. Longitudinal studies with larger cohorts, taking into account the dimensional nature of aggressiveness, are needed to better understand the underlying neurobiology.

1. Introduction

Human aggression is a complex and multifactorial construct

(Dorfman et al., 2014) with multiple motives and triggers (Wahlund and Kristiansson, 2009), including aspects of anger, impulsivity, and self-control (Schutter and Harmon-Jones, 2013). It is defined as any type

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of hostile, injurious, or destructive behavior (Siever, 2008) directed towards other people or living beings that causes them physical harm or mental distress (Anderson and Bushman, 2002; Perach-Barzilay et al., 2013). Aggression ranges from mild irritability to overtly violent behavior (Blair, 2016; Rosell and Siever, 2015). In its most extreme form, aggressive behavior can lead to serious crimes with significant physical/emotional consequences for the victims and impose substantial costs to society (Dambacher et al., 2015; Peper et al., 2015; Zhang et al., 2019). Therefore, a deeper examination of the factors associated with aggressive behavior is essential in order to understand the underlying neural mechanisms and develop effective prevention and targeted treatment interventions (Waller et al., 2017).

Over the past few decades, neuroimaging techniques have been developed to provide insight into the neural substrates of behavior by observing structure and function of the living brain (Keedy et al., 2019). For aggression, functional magnetic resonance imaging studies have shown neuronal changes in brain regions associated with reward approach and inhibitory control, including the orbitofrontal and ventromedial prefrontal cortex (PFC) (Blair, 2017; Waller et al., 2015), and dysfunction in areas that process/regulate emotion, including the amygdala and the anterior cingulate cortex (Coccaro et al., 2007; Hyde et al., 2014). There is also an association with reduced functional connectivity between these regions during socio-emotional processing (Contreras-Rodriguez et al., 2015; Marsh et al., 2011) and at rest (Motzkin et al., 2011; Philippi et al., 2015) (see Nikolic et al., 2022; Wong et al., 2019 for *meta*-analyses).

For a deeper understanding, analyzing structural connections between brain regions implicated in aggression offers the potential to move beyond theories of regional dysfunction to a more coherent understanding of the underlying brain networks (Craig et al., 2009; Waller et al., 2017). However, there are few data on how individual differences in white matter (WM) microstructure, the anatomical basis of connections in such networks, relate to aggressive tendencies (Karlsgodt et al., 2015; Sundram et al., 2012). Diffusion tensor imaging (DTI) is a suitable non-invasive imaging technique for this purpose (Lederer et al., 2016; Shin et al., 2014). By measuring the diffusion of water within each voxel, various parameters can be estimated: Fractional anisotropy (FA) is calculated from the eigenvalues of the diffusion tensor and reflects the diffusion of water molecules along the fiber tract (Beaulieu, 2002). Higher FA values indicate more directional coherence of diffusion within tracts, which is interpreted as "greater integrity" (Basser et al., 1994; Thomason and Thompson, 2011). Axial diffusion (AD) measures the diffusion of water molecules along the major axis of nerve fibers (Christian Beaulieu, 2002; Budde et al., 2009), i.e. it quantifies how freely water molecules can diffuse along the length of the axons. High AD values indicate free diffusion, typically found in healthy, wellmyelinated axons (Budde et al., 2009). The mean diffusion (MD) value is a direction-independent measure of the overall diffusion of water molecules in each voxel (Christian Beaulieu, 2002), based on the average of the three main diffusion directions (Asken et al., 2018). MD is inversely related to WM connection quality (Soares et al., 2013), so lower values indicate good fiber bundle integrity (Beaulieu, 2009). Conversely, higher values indicate a lack of barriers to water diffusion (Le Bihan et al., 2001).

Recent DTI studies have shown an association between higher levels of self-reported aggression and reduced frontal lobe WM integrity in psychiatric disorders, such as lower FA in the inferior frontal WM in men with schizophrenia (e.g., Hoptman et al., 2002), reduced FA and increased MD in the right frontal lobe in men with antisocial personality disorder (e.g., Sundram et al., 2012), or reduced FA in the callosal genu and anterior commissure in youths with bipolar disorder (e.g., Saxena et al., 2012). Studies of incarcerated men (e.g., Motzkin et al., 2011; Wolf et al., 2015) link psychopathy to reduced structural integrity, particularly in the right uncinate fasciculus (UF) - the reciprocal connection between the ventromedial PFC and the anterior temporal lobe (Von Der Heide et al., 2013). Findings suggest that aggressive behavior is associated with greater diffusivity in a variety of WM tracts like the UF, inferior fronto-occipital fasciculus, cingulum, corticospinal tract, thalamic radiations, and the corpus callosum (see Waller et al., 2017 for a review).

Previous research suggests that aggressive behavior is dimensional in nature (Krueger et al., 2007; Olson-Ayala and Patrick, 2018), highlighting the need to test these relationships across the distribution of aggressive behavior ranging from low to clinical. Current literature is mainly based on patient populations with complex syndromes (Beyer et al., 2014). Although a subset of individuals with mental illness may exhibit increased aggression, the majority of violent acts are committed by those without psychiatric diagnoses, as mental illness affects a relatively small percentage of the population (Walsh et al., 2002). Clinical findings provide valuable insights, but they are complicated by the fact that changes associated with aggression occur in the context of diseaserelated changes, and may therefore be difficult to isolate (Karlsgodt et al., 2015). In addition, this line of research has generally been affected by small/selective samples, inconsistent diagnostic criteria, and a lack of replication. Variables such as chronological age (Lebel et al., 2012; Lebel and Beaulieu, 2011), body weight (Xu et al., 2013), physical activity level (Gow et al., 2012), intelligence level (Yu et al., 2008), and drug/ alcohol use (Lederer et al., 2016) affect WM integrity and have not been adequately controlled for. Other confounders include medication effects, comorbid psychiatric diagnoses, and psychopathic traits (e.g., Pape et al., 2015; White et al., 2008).

The relationship between WM integrity and aggression has rarely been examined in healthy community samples. Beyer et al. (2014) found no association between structural connectivity of the orbitofrontal cortex with the amygdala and trait aggression in a sample of 93 healthy men, arguing against a direct relationship between this fronto-limbic connection and aggression. Another study found that higher MD within the fronto-temporal-subcortical network was associated with increased expressive aggression forms in 258 participants ranging from childhood to young adulthood, suggesting that aggressive tendencies are subcortically driven (Peper et al., 2015). Sobhani et al. (2015) reported a negative relationship between psychopathic traits and UF microstructural integrity in 24 young men, supporting the idea of altered amygdala-ventromedial PFC connectivity with elevated psychopathic traits. Using tract-based spatial statistics (TBSS), (Karlsgodt et al., 2015) observed a significant relationship between verbal and physical aggressiveness and WM integrity in parietal brain areas in 45 young participants.

Although few studies examine community samples, current research lacks appropriate control groups. In this study, we examine, for the first time, diffusion-based WM measures in two samples of healthy individuals with no psychiatric history but different propensities for aggressive behavior. We chose to study high-contact athletes (martial artists) as one experimental group because they engage in aggressive behavior in a socially accepted way. This is a type of sport where aggression is an essential part of performance (Pačesová and Šmela, 2020) due to the necessity of fighting and competition (Basiaga-Pasternak et al., 2020). As differences between men and women have been shown for WM measures (Inano et al., 2011; Koolschijn and Crone, 2013) and physical aggression scores (Archer, 2004; Buss and Perry, 1992), we limit our study to male participants. We use a whole-brain TBSS approach to identify pathways where martial artists show altered WM integrity compared to healthy controls. We hypothesize that (1) martial artists have higher physical aggressiveness scores than control subjects and that (2) martial artists have reduced WM integrity compared to controls.

2. Material and methods

The comprehensive multimodal study spanned two days and is described in detail in <u>Seidenbecher et al. (2023)</u>. Here, we focus on the methodological aspects pertinent to our current study.

2.1. Sample

A total of 33 martial artists and 38 control subjects from the local general population participated in the present study. Exclusion criteria were age <18 or >50 years, female or diverse gender, left-handed or ambidextrous, history of neurological or psychiatric disorders including alcohol/substance dependence, self-reported history of delinquency, head injury with loss of consciousness, and MRI contraindications. For martial artists, the inclusion criteria were at least one year of martial arts experience and regular training at the time of measurement. Additionally, only "hard" martial arts (in the sense of full-contact combat sports, such as mixed martial arts (MMA), (kick-)boxing, and Muay Thai) were considered for inclusion, specifically sports characterized by kicking and punching techniques and kumite (a type of sparring) (Nosanchuk 1981; Vertonghen et al. 2014). A subset of controls also engaged in recreational sports (other than martial arts), such as soccer, floor hockey, or dancing.

Three participants (n = 2 martial artists) were excluded because they were ambidextrous. Another n = 3 participants (n = 1 martial artist) were excluded because of frequent drug use. One martial artist was excluded for not practicing martial arts regularly at the time of measurement. In addition, n = 1 control subject was excluded because of slight martial arts experience (3 months), and n = 2 control subjects were excluded because they reported participating in fights within the local soccer ultras scene. The final sample consisted of n = 29 martial artists and n = 32 controls.

All participants gave written informed consent prior to enrollment in accordance with procedures approved by the Institutional Review Board of the Faculty of Medicine (Otto von Guericke University Magdeburg). They received financial compensation for their participation. The study was conducted in accordance with the ethical guidelines of the World Medical Association (Declaration of Helsinki).

2.2. Measures

2.2.1. Physical aggression

The Buss-Perry Aggression Questionnaire (BPAQ; Cronbach's α = 0.62-0.82, Werner and von Collani, 2014) was used in this study as a real-life measure of aggressive and violent behavioral traits (Archer and Webb, 2006; Karlsgodt et al., 2015; Krämer et al., 2011). The BPAQ consists of 29 items rated on a four-point Likert scale ranging from 1 -"not applicable" to 4 – "completely applicable". It includes the subscales "physical aggression" (tendency to use threats and/or physical harm to others and objects) and "verbal aggression" (disagreements and argumentative behavior), which reflect behavioral tendencies in the form of reactive aggression, as well as the further subscales "anger" (irritability and temper control; affective component) and "hostility" (feelings of jealousy, suspicion, and resentment; cognitive component) (Buss and Perry 1992; Werner and von Collani 2014). As indicated in previous studies (Karlsgodt et al. 2015), we additionally computed the two composite scores for "aggressive actions" (physical + verbal aggression) and "aggressive thoughts" (anger + hostility).

The Appetitive and Facilitative Aggression Scale (AFAS; work in progress, civilian version of the Appetitive Aggression Scale (Cronbach's $\alpha = 0.85$, Weierstall and Elbert, 2011)) consists of 30 items that ask about reactions to frustrations or injustices over the course of one's life, which must be rated on a five-point Likert scale ranging from 0 - "never" to 4 - "very often", and which can be divided into two subscales, 'appetitive aggression' and 'facilitative aggression'. Appetitive aggression (e.g., item 7: "Did you provoke others just for the fun of it?") refers to the intrinsic motivation to seek and derive pleasure, arousal, and a sense of control from both witnessing and engaging in aggressive or violent behavior, regardless of external threats (Crombach and Elbert, 2015; Weierstall and Elbert, 2011). Facilitative aggression (e.g., item 1: "Have you ever kicked or thrown an object in frustration?") is a reactive form of aggression that occurs spontaneously in response to an

immediate perceived threat or danger (Elbert et al., 2010).

2.2.2. Further measures

Right-handedness was confirmed using the Edinburgh Handedness Inventory (Oldfield, 1971). Crystallized and fluid intelligence were assessed using the Multiple-Choice Vocabulary Intelligence Test (Lehrl, 2005) and Subtest 3 of the Performance Testing System (Horn, 1983). Metabolic equivalent (MET), as assessed by the Global Physical Activity Questionnaire (GPAQ; WHO, 2005), is used to indicate physical activity intensity. The absence of past psychiatric or personality disorders was assessed using the Brief Psychiatric Rating Scale (CIPS, 1977) and the Structured Clinical Interview for DSM-IV Axis II Personality Disorders (Fydrich et al., 1997).

2.3. MRI acquisition

Data were acquired using a 3 Tesla Siemens MRI scanner (MAGNE-TOM Prisma syngo MR D13D; Siemens, Erlangen, Germany) with a 64channel phased-array head coil.

The DTI sequence consisted of a spin-echo diffusion-weighted echo planar imaging (EPI) sequence acquired in the axial plane using simultaneous multi-slice image acceleration. An isotropic resolution of $1.8 \times 1.8 \times 1.8 \text{ mm}^3$ was used with repetition time (TR) = 3890 ms, echo time (TE) = 64.20 ms, echo spacing = 0.57 ms, EPI factor = 120, and bandwidth = 2084 Hz/Px. A total of 60 diffusion directions with b-values of 1000 s/mm² and 2000 s/mm² were used, and 15b = 0 images were obtained (interleaved throughout the acquisition). A multi-band acceleration factor of 2 was used with generalized autocalibrating partially parallel acquisition (GRAPPA; (Griswold et al., 2002; Skare et al., 2008) of 2. The scan was performed twice with phase encoding in the anterior-posterior and then posterior-anterior direction for a total acquisition time of 18 min 48 s.

Structural images were acquired using a magnetization-prepared rapid gradient echo (MPRAGE) sequence. High-resolution T1-weighted three-dimensional anatomical scans of 192 sagittal slices with a voxel size of $1.0 \times 1.0 \times 1.0 \text{ mm}^3$ of the whole brain were obtained (TR = 2500 ms, TE: 2.82 ms, field of view (FOV) from foot to head (FH): 256 mm, anterior to posterior (AP): 256 mm and right to left (RL): 192 mm, flip angle of 7°, matrix size = 256 × 256). The scan time required for structural acquisition was 9 min 20 s.

2.4. DTI processing

2.4.1. Preprocessing

The entire diffusion dataset was then denoised using the MRtrix3 (Tournier et al., 2019) tool *dwidenoise* (Veraart et al., 2016), and Gibbs ringing was corrected using *mrdegibbs* (Kellner et al., 2016). After that the diffusion data were processed using the Functional Magnetic Resonance Imaging of the Brain Software Library (FSL, version 6.0.6.4; Oxford, UK). The preprocessing steps included the commands *TOPUP & eddy* (Andersson et al., 2003; Andersson and Sotiropoulos, 2016) to correct for distortions caused by magnetic field inhomogeneities, eddy currents and motion artifacts respectively. AD/FA/MD images were generated using *DTIFIT* and checked for the presence of artifacts.

2.4.2. Tract-based spatial statistics

To evaluate group differences in the diffusion measures between the martial artists and controls, voxel-wise statistical analysis was performed using TBSS. To enable voxel-wise statistics, subject data were first fitted to the individual T1 volume, then to a T1 study template created using *Advanced Normalization Tools (ANTS; Avants et al., 2009)*, and finally transferred to the Montreal Neurological Institute (MNI) space using *ANTS*. To compare AD, FA or MD between the groups, two-sample unpaired t-tests were performed using permutation tests with 5000 permutations and threshold-free cluster enhancement (TFCE) implemented in the FSL submodule *Randomise*. Graphical presentation of results was performed using FSLeyes software (version: 1.6.1; Oxford, UK). The *tbss_fill* script implemented in FSL was used to thicken the results for better visualization.

Correlation analyses between the diffusion measures and the behavioral data were computed by using a general linear model to estimate the positive and negative associations of AD, FA or MD across participants with the four aggression scores using *Randomise*. 5000 permutations per contrast were calculated and TFCE was performed. Finally, a cluster analysis was performed in the regions where there were group differences.

2.4.3. Region of interest analysis

In addition, we performed a region of interest (ROI) analysis to examine changes in specific WM tracts based on current literature (see Supplementary material S1 for detailed description).

2.5. Statistical analysis

SPSS Statistics (version 28.0.1.0; IBM, Armonk, NY, USA) and R (version 4.3.1, (R Core Team, 2022) were used for statistical analyses of demographics. All data were tested for normal distribution using Shapiro-Wilk tests. Two-sample t-tests and Pearson correlations were performed for normally distributed data (p > 0.05), otherwise, Mann-Whitney U tests and Spearman correlations were performed. Chi-squared or Fisher's exact tests were used to analyze categorical variables.

Partial correlation analyses were used to examine the associations between the extracted median diffusion values of the tracts with significant group differences and the four physical aggression scores (AFAS: \sum appetitive aggression, physical appetitive aggression; BPAQ: physical aggression, aggressive actions). Age was controlled for, and the p-values were adjusted using the false discovery rate (FDR;Benjamini and Hochberg, 1995) correction method.

3. Results

3.1. Descriptive data

Martial artists and controls did not differ significantly in age (T(59)= -1.58, p = 0.119), highest level of education (p = 0.059), and crystalline (U = 426.00, Z = -0.55, p = 0.582) or fluid (T(59) = -1.04, p =0.301) IQ scores. In addition, there were no significant differences between the two groups in handedness (U = 404.50, Z = -0.89, p =0.376), Body Mass Index (BMI; U = 456.00, Z = -0.12, p = 0.908), weight (t(59) = 0.32, p = 0.752), alcohol use (U = 315.00, Z = 1-0.16, p = 0.247) and physical activity (U = 371.00, Z = -1.34, p = 0.179). There was no evidence of psychiatric symptoms, psychopathic traits, or early childhood stress in the present sample (see Supplementary material S2). All participants reported being physically healthy and never having received psychological or neurological treatment. Six participants reported taking medication at the time of measurement: n = 2antihistamines (n = 2 martial artists), n = 2 thyroid hormones (iodide, Lthyroxin; n = 1 martial artist), n = 2 bronchodilators (inhalation powder; n = 2 martial artists). Regarding nicotine use (n = 4 martial artist, n = 5 control subjects), there was no significant association between group membership and smoking, $\chi^2(1) = 0.041, p = 0.840$. Table 1 provides an overview of the sample characteristics.

Martial artists reported a median martial arts experience of Mdn = 11.50 years (Q1 = 6.85, Q3 = 17.00). N = 21 of them had participated in fights (Mdn = 6.00 times, Q1 = 3.00, Q3 = 20.00).

Both groups reported comparable personal experiences with violence $(\chi^2(1) = 2.63, p = 0.105)$. Martial artists scored significantly higher on the AFAS *appetitive aggression* (U = 161.50, Z = -4.39, p < 0.001) and *physical appetitive aggression* (U = 99.00, Z = -5.56, p < 0.001) scales, as well as on the BPAQ *aggressive actions* (U = 180.00, Z = -4.11, p < 0.001) and *physical aggression* (U = 147.50, Z = -4.59, p < 0.001) scales.

Table 1

Sample characteristics of the martial artists compared to controls.

	Martial artists $(n = 29)$	Controls ($n =$ 32)	Statistics	
Age [years]	$M = 25.59 \pm 5.74$	$M=28.00\pm 6.14$	t(59) = -1.58, p = 0.119	
Highest level of education [n]			p = 0.059	
 lower secondary school 	n = 1			
 secondary school 	n = 6	n = 2		
 high-school diploma 	n = 14	n = 12		
 polytechnic/ university degree 	n = 8	n = 18		
Handedness (FHI)	Mdn = 90.00	Mdn = 80.00	U = 40450 Z =	
Hundedness (EHI)	01 - 70.00 03	01 - 70.00 03	-0.89	
	= 100.00	= 100.00	n = 0.376	
BMI [kg/m ²]	Mdn = 24.49	Mdn = 24.88	U = 456.00 Z =	
2000 [006/ 00]	01 = 23.02, 03	01 = 22.09, 03	-0.12, p = 0.908	
	= 26.34	= 26.93	, , , , , , , , , , , , , , , , , , ,	
Weight [kg]	M = 82.76, SD	M = 81.75, SD	t(59) = 0.32, p =	
0 - 0-	= 11.68	= 12.96	0.752	
Alcohol use [g/week]	Mdn = 4.75	Mdn = 12.25	U = 315.00, Z =	
	Q1 = 0.00, Q3 =	Q1 = 3.75, Q3	-1.16,	
	24.75	= 24.00	p = 0.247	
Physical activity	Mdn = 4980.00	Mdn = 4010.00	U = 371.00, Z =	
(MET)	Q1 = 2920.00,	Q1 = 2460.00,	-1.34,	
	Q3 = 10300.00	Q3 = 7500.00	p = 0.179	
Crystallize	Mdn = 104.00	Mdn = 101.00	U = 426.00, Z =	
intelligence (MWT-	Q1 = 100.00,	Q1 = 97.75, Q3	-0.55,	
B, IQ)	Q3 = 115.00	= 112.00	p = 0.582	
Fluid intelligence	$M=114.90~\pm$	$M=117.47~\pm$	t(59) = -1.04, p	
(LPS-3, IQ)	9.19	9.98	= 0.301	

Notes. BMI = Body Mass Index; EHI = Edinburgh Handedness Inventory (Old-field, 1971); IQ = intelligence quotient; LPS-3 = Performance Testing System, subtest: logical thinking (Horn, 1983); *Mdn* = median; MET = metabolic equivalent; MWT-B = Multiple-choice Vocabulary Test (Lehrl, 2005), version B; n = number; Q1 = first quartile; Q3 = third quartile.

 Table 2

 Intramural characteristics of the martial artists compared to controls.

	Martial artists $(n = 29)$	Controls ($n =$ 32)	Statistics
Victim of violence			$\chi^2(1) = 2.63, p =$
– yes	n = 14	n = 9	0.105
– no	n = 15	n = 23	
AFAS			U = 161.50, Z =
appetitive	Mdn = 8.00	Mdn = 2.50	$-4.39, p < 0.001^{***}$
aggression (Σ)	Q1 = 6.00, Q3	Q1 = 0.25, Q3	U = 99.00, Z =
	= 12.50	= 5.75	$-5.56, p < 0.001^{***}$
physical appetitive	Mdn = 3.00	Mdn = 0.00	
aggression	Q1 = 1.50, Q3	Q1 = 0.00, Q3	
	= 5.50	= 0.00	
BPAQ			U = 180.00, Z =
aggressive actions	Mdn = 28.00	Mdn = 22.50	$-4.11, p < 0.001^{***}$
(Σ)	Q1 = 25.00,	Q1 = 19.25, Q3	
	Q3 = 32.00	= 26.00	
physical aggression	Mdn = 16.00	Mdn = 12.00	U = 147.50, Z =
	Q1 = 14.00,	Q1 = 10.25, Q3	$-4.59, p < 0.001^{***}$
	Q3 = 21.50	= 14.75	
Psychopathy ^a	M = 295.28,	M = 285.00,	t(59) = 1.59, p =
	SD = 27.10	SD = 23.27	0.117

Notes. AFAS = Appetitive and Facilitative Aggression Scale (work in progress, civil version of Appetitive Aggression Scale (AAS, (Weierstall and Elbert, 2011)); BPAQ = Buss-Perry Aggression Questionnaire (Werner and von Collani, 2014); Mdn = median; n = number; Q1 = first quartile; Q3 = third quartile; Σ = sum score.

^a Recorded using Psychopathic Personality Inventory-Revised (Alpers and Eisenbarth, 2008).

The two groups did not differ in the general expression of the personality trait 'psychopathy' (t(59) = 1.59, p = 0.117), as the mean values for both groups fell within the average normal range. Table 2 provides an overview of the intramural characteristics when comparing the two groups.

In terms of general morphological brain differences, martial artists and controls did not differ in total intracranial volume (TIV; T(59) = 0.13, p = 0.895) or in total WM volume (T(58) = -0.37, p = 0.715).

3.2. TBSS analysis

There were no significant effects when comparing the FA of martial artists and control subjects.

Martial artists showed significant clusters of increased MD in eight WM tracts compared to controls, including portions of the corpus callosum (body and splenium), the left corona radiata (superior and posterior portions), and the left superior longitudinal fasciculus (SLF) ($p_{TFCE-corr} < 0.05$, >20 contiguous voxels). See Table 3 for detailed information and Fig. 1 for visualization.

Positive associations between physical appetitive aggression and median MD values are evident for the following tracts: body of corpus callosum (r = 0.33, p = 0.012), splenium of corpus callosum (r = 0.45, p = 0.004), left anterior limb of internal capsule (r = 0.36, p = 0.009), left superior corona radiata (r = 0.38, p = 0.009), left posterior corona radiata (r = 0.42, p = 0.005), left posterior thalamic radiation (r = 0.40, p = 0.008), and left superior longitudinal fasciculus (r = 0.36, p = 0.009) (see Supplementary material S3 for detailed information on the clusters of positive associations). No other association effects were found with any of the aggression scales.

When comparing AD in martial artists and controls, several significant clusters were found in 34 different WM tracts ($p_{TFCE-corr} < 0.05$, >20 contiguous voxels). Detailed information for all significant clusters is shown in Table 4, while Fig. 2 provides a graphical representation.

Positive associations between \sum appetitive aggression and median

Table 3

Significant clusters of voxels within gyral or subcortical WM on the TBSSderived MD skeletons where martial artists > healthy controls. Results show peak x, y and z coordinates, cluster size (minimum number of voxels: 20), TFCE corrections for searching the entire skeleton (p < 0.05) and the effect size (Cohen's d) for each regional finding.

White matter region [label]	Coordinates of peak location		Cluster size (number of	TFCE- corrected	Cohen's d	
	x	у	z	voxels)	p-value	
Body of corpus callosum [4]	-12	-13	30	59	0.049*	0.63
Splenium of	-24	-58	14	106	< 0.05*	0.51
corpus callosum [5]	-15	-45	22	85	<0.05*	0.81
Anterior limb of internal capsule, L [18]	-16	13	-3	86	<0.05*	1.18
Superior corona	-19	-20	38	136	0.048*	0.80
radiata, L [26]	-26	$^{-20}$	33	22	< 0.05*	0.76
Posterior corona	$^{-20}$	-28	38	40	0.049*	0.63
radiata, L [28]	-23	-49	27	38	0.049*	0.86
Posterior thalamic radiation ^a , L [30]	-26	-57	15	33	<0.05*	0.75
Superior longitudinal fasciculus, L [42]	-31	-20	33	46	<0.05*	0.80
Tapetum, L [50]	-26	-48	19	38	<0.05*	0.76

Notes. L = left, TFCE = threshold-free cluster enhancement. Atlas: JHU ICBM-DTI-81 White-Matter (Oishi et al., 2008).

^a Include optic radiation

AD values are evident for the following tracts: genu of corpus callosum (r = 0.34, p = 0.012), splenium of corpus callosum (r = 0.40, p = 0.005), and right anterior corona radiata (r = 0.30, p = 0.020). Positive associations between physical appetitive aggression and median AD values are evident for the following tracts: body of corpus callosum (r = 0.41, p = 0.002), splenium of corpus callosum (r = 0.43, p < 0.001), left retrolenticular part of internal capsule (r = 0.45, p < 0.001), right superior corona radiata (r = 0.53, p < 0.001), and left posterior corona radiata (r = 0.36, p = 0.005) (see Supplementary material S3 for detailed information on the clusters of positive associations). No other association effects were found with any of the aggression scales.

4. Discussion

For the first time, we describe the relationship between WM integrity and aggressiveness in two healthy male community samples, differing only in their propensity for aggressive behavior. Martial artists, who exhibited higher levels of appetitive and physical aggression than controls, showed increased MD in parietal and occipital regions and widespread increased AD in frontal, parietal, and temporal cortices. Median AD/MD values across participants were significantly positively associated with both physical appetitive aggression and summed appetitive aggression in several clusters, including the corpus callosum, the corona radiata, and the superior longitudinal fasciculus.

We found increased MD in parts of the corpus callosum, the brain's largest fiber tract, essential for interhemispheric communication (Lindner et al., 2016; Menks et al., 2017). The body of the corpus callosum is crucial for emotion regulation (Raine et al., 2003) playing an important role in dysregulated affect, leading to higher aggressive tendencies (Dailey et al., 2018). Sundram et al. (2012) also reported increased MD in the corpus callosum in patients with APD. We found increased MD in the anterior limb of the internal capsule and in the corona radiata. The anterior limb of the internal capsule contains fibers that project from the thalamus through the anterior corona radiata to the frontal lobe (Karababa et al., 2015), fibers linked to impaired top-down emotion regulation in bipolar disorder (Singh et al., 2013). WM in these regions may play a role in impulsive aggression (Reich et al., 2019). We found MD increases in the SLF, which connects parietotemporal areas to the frontal lobe. Lower FA in the SLF is associated with impulsive aggression in intermittent explosive disorder (Lee et al., 2016).

The broader distribution of increased AD in martial artists compared to controls aligns with findings that antisocial behavior in adults is linked to greater diffusivity in various WM tracts (Waller et al., 2017). Besides increases in the aforementioned regions (e.g., corpus callosum, corona radiata, and SLF), martial artists show higher AD values in the corticospinal tract compared to controls. FA in the corticospinal tract correlates positively with motor impulsivity (Goldwaser et al., 2022). Significant effects were also noted in the fornix, linked to impulse dyscontrol (Gill et al., 2021), and in the superior fronto-occipital fasciculus, associated with nonplanning impulsivity (Goldwaser et al., 2022). AD measures can be biased by noise, making MD, which incorporates all three eigenvalues, a more reliable indicator of WM microstructure.

No significant effects were found for FA between martial artists and controls. FA measures the directionality of water diffusion in tissues (Beaulieu, 2002). In contrast, AD and MD may indicate more specific changes in microstructural integrity, such as demyelination (Budde et al., 2009) axonal damage (Song et al., 2005), or reduced tissue density (Soares et al., 2013). These changes can occur without affecting diffusion directionality if overall fiber alignment is preserved (Wheeler-Kingshott and Cercignani, 2009). While increased AD may indicate more efficient axonal transport (Budde et al., 2009), increased MD is often associated with tissue damage (Soares et al., 2013). The simultaneous increase in both parameters in martial artists compared to controls may reflect a combination of their brain circuitry more focused on complex motion (increased connectivity), which may explain their interest in martial arts and subtle microstructural changes due to repetitive impacts



Fig. 1. TBSS results comparing MD for martial artists > controls (red-yellow highlighted). In the background, the FA skeleton is marked in green. Images are shown according to radiological orientation. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

(increased extracellular water content with relatively intact axons). Based on our correlation analysis, the described differences in AD and MD also seem to be partly related to appetitive aggression, the hedonistic driven motivation for aggression.

Contrary to studies on psychopathy (Craig et al., 2009; Motzkin et al., 2011) or conduct disorder (Rubia et al., 2009; Sarkar et al., 2013), we found no differences in MD or AD of the UF. Structural prefrontalamygdala connectivity deficits appear specific to psychiatric/forensic populations (Beyer et al., 2014). Instead, we observed widespread WM integrity changes across various tracts. Waller et al. (2017) also found that aggressive behavior reflects WM dysfunction across regions and hemispheres, not a specific UF abnormality. We could not confirm the right hemisphere lateralization effects described in APD (Sundram et al., 2012).

It is unclear whether increased aggression in healthy individuals is linked to the same neurostructural changes found in patient/forensic samples (Karlsgodt et al., 2015). Inconsistencies between previous studies and our study may result from different methodologies (Passamonti et al., 2012). First, sample differences are evident. Most studies assess forensic male participants (Waller et al., 2017), where a history of institutionalization or substance abuse may explain anatomical differences (Craig et al., 2009). Psychopathic traits also moderate effects (Waller et al., 2017), which we controlled for. In a study of incarcerated men, lower FA in the right UF was specific for those with psychopathy compared to those without (Motzkin et al., 2011). Second, well-established age-related changes in brain structure complicate the interpretation of WM differences in youth or samples with a wide age range and aggressive behavior (Waller et al., 2017). Brain maturation continues beyond infancy, and adolescence is thought to be a key period of brain rewiring (Lebel and Beaulieu, 2011). Age-related effects on WM are evidenced by an increased WM integrity associated with chronological age (Asato et al., 2010; Lebel et al., 2012; Lebel and Beaulieu, 2011; Simmonds et al., 2014). Fronto-temporal connections, such as the UF and SLF, show a more prolonged maturation (Lebel et al., 2012), with the UF reaching its developmental peak in the third decade of life (Lebel et al., 2008, 2012; Lebel and Beaulieu, 2011). We did not detect UFspecific effects, possibly due to including age as a iate, in contrast to previous studies. Further research with larger sample sizes and a broader age range is needed to elucidate the relationship between WM pathway development and aggressive behavior. In addition, controlling for age is essential. Different analysis methods (e.g., TBSS vs. tractography) and different diffusion parameters (e.g., FA vs. AD vs. MD vs. radial diffusivity) may explain differences (Zhang et al., 2014). Differences in image acquisition protocols may also contribute to discrepancies.

Martial artists show increased MD and AD in several brain regions compared to controls. This may be explained by changes in WM integrity associated with aggression, which is also supported by positive correlations of AD/MD with (physical) appetitive aggression. Several studies show increased aggression in full-contact martial arts competitors (Jarvis, 2003; Rydzik, 2022), also compared to other athletes and nonathletes (Boostani and Boostani, 2012). However, regular practice of martial arts over many years with respect to rules and regulations reduces excessive aggression and tension (Ambroży et al., 2015; Kotarska et al., 2019; Kuśnierz et al., 2014). Although the developmental effects of martial arts remain controversial (Lee and Lim, 2019), our data clearly show significantly higher aggression scores in martial artists compared to controls. The BPAQ, particularly the verbal and physical subscales, correlates with measures of violent behavior toward others/ self (Archer and Webb, 2006; Bushman and Wells, 1998; Zhang and Lu, 2012) and serves as a good index of real-life aggressive behavior (Karlsgodt et al., 2015). In addition, we have carefully selected participants from hard martial arts because of their higher aggression compared to traditional martial arts (Kostorz and Sas-Nowosielski, 2021). Thus, differences in WM integrity between martial artists and controls may be partly due to their differences in aggression.

Another explanatory approach is adaption due to training. Long-term or frequent training affects brain plasticity in athletes (Yarrow et al., 2009), suggesting that differences between martial artists and controls could be due to different physical activities. These structural adaptations may reflect more efficient neuronal connectivity and thus increased diffusivity. However, the groups did not differ in self-reported physical activity intensity (MET).

Another important consideration is concussion. The brain's WM is vulnerable to injury from concussive impacts, which cause stretching of WM fibers and lead to changes in structural integrity (Lancaster et al., 2018). Given the chronic, cumulative effects of repeated blows to the

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Table 4

Significant clusters of voxels within gyral or subcortical WM on the TBSS-derived AD skeletons where martial artists > healthy controls. Results show peak x, y and z coordinates, cluster size (minimum number of voxels: 20), TFCE corrections for searching the entire skeleton (p < 0.05) and the effect size (Cohen's d) for each regional finding.

White matter region [label]	Coordinates of peak location		location	Cluster size (number of voxels)	TFCE-corrected p-value	Cohen's d
	x	у	Z	-		
Middle cerebellar peduncle [1]	-6	-19	-32	265	0.014*	0.60
Genu of corpus callosum [3]	12	27	-8	242	0.023*	0.29
1	-14	21	24	47	0.010*	0.42
Body of corpus callosum [4]	-18	-20	35	792	0.009**	0.47
• • •	12	-30	25	260	0.014*	0.42
	8	19	18	150	0.025*	0.39
Splenium of corpus callosum [5]	-8	-39	12	1572	0.010*	0.74
Corticospinal tract, L [8]	-9	$^{-18}$	-22	172	0.010*	0.46
Medial lemniscus, R [9]	7	-33	-26	31	0.042*	0.41
Superior cerebellar peduncle, L [14]	-6	-24	-22	42	0.022*	0.37
Cerebral peduncle, L [16]	$^{-10}$	$^{-10}$	-13	331	0.010*	0.81
Anterior limb of internal capsule, R [17]	22	-1	18	369	0.022*	0.68
Anterior limb of internal capsule, L [18]	$^{-10}$	-1	2	399	0.010*	0.87
Posterior limb of internal capsule, R [19]	13	-2	4	113	0.023*	0.41
	25	-20	17	49	0.018*	0.25
Posterior limb of internal capsule, L [20]	-23	-20	0	527	0.010*	0.57
Retrolenticular part of internal capsule, R [21]	31	-25	3	412	0.021*	0.78
Retrolenticular part of internal capsule, L [22]	-24	-20	0	403	0.010*	0.69
Anterior corona radiata, R [23]	12	28	$^{-12}$	528	0.023*	0.94
	26	28	18	239	0.014*	0.83
	17	26	27	27	0.014*	0.47
	18	36	20	21	0.014*	0.33
Anterior corona radiata, L [24]	-22	27	21	462	0.008**	0.84
	-19	28	15	417	0.010*	0.62
	-16	39	-2	88	0.010*	0.33
Superior corona radiata, R [25]	27	-17	28	1039	0.014*	0.88
Superior corona radiata, L [26]	-19	-22	37	909	0.008**	0.97
	-26	-23	20	28	0.010*	0.33
Posterior corona radiata, R [27]	19	-33	35	90	0.018*	0.55
	25	-28	29	72	0.016*	0.60
	27	-54	21	59	0.014*	0.52
	25	-49	24	40	0.014*	0.31
	27	-24	20	29	0.018*	0.29
	32	-56	19	24	0.019*	0.46
Posterior corona radiata, L [28]	-27	-38	19	204	0.010*	0.66
	-20	-29	37	32	0.009	0.42
	-19	-40	38	21	0.021*	0.44
Posterior thalamic radiation ^a , R [29]	37	-51	-3	534	0.019*	0.74
Posterior thalamic radiation ^a , L [30]	-34	-56	-3	505	0.016*	0.63
Sagittal stratum ⁰ , R [31]	41	-40	-7	113	0.019*	0.73
Sagittal stratum ⁹ , L [32]	-39	$^{-28}$	-6	129	0.010*	0.43
	-44	-30	-14	78	0.025*	0.51
	-35	-53	-6	73	0.016*	0.74
External capsule, R [33]	33	-14	5	135	0.023*	0.53
External capsule, L [34]	-30	-6	14	147	0.010*	0.72
	-29	-20	13	117	0.014*	1.02
	-32	-21	-1	22	0.013*	0.54
Fornix (crew)/Stria terminals, R [39]	32	-27	-4	78	0.022*	0.63
Fornix (crew)/Stria terminals, L [40]	-33	-17	-12	86	0.014*	0.67
Superior longitudinal fasciculus, R [41]	43	-8	24	423	0.021*	0.79
	40	-50	8	241	0.021^	0.75
Consider the standing of Graning Loss T. [40]	32	-18	34	36	0.017*	0.18
Superior longitudinal rasciculus, L [42]	-36	-44	18	180	0.01/*	0.83
	-34	5	21	88	0.032*	0.55
	-32	-12	21	55	0.031*	0.56
	-29	-23	36	49	0.009	0.51
	-43	-50	2	20	0.019*	0.31
Comparing fromto posizital (control of D 5407	-31	-1	18	25	0.032^	0.40
Superior fronto-occipital fasciculus", R [43]	22	0 7	20	4/	0.021^	0.53
Superior fronto-occipital fasciculus", L [44]	-21	/	19	25	0.019*	0.30
Interior fronto-occipital fasciculus, R [45]	28	8	-10	0/	0.025^	0.8/
menor fromo-occipital fasciculus, L [46]	-34	-11	-13	04	0.014"	0.44

Notes. L = left, R = right, TFCE = threshold-free cluster enhancement. Atlas: JHU ICBM-DTI-81 White-Matter (Oishi et al., 2008).

^a Include optic radiation
 ^b Include inferior longitudinal fasciculus and inferior fronto-occipital fasciculus.

^c Could be a part of anterior internal capsule.



Fig. 2. TBSS results comparing AD for martial artists > controls (red-yellow highlighted). In the background, the FA skeleton is marked in green. Images are shown according to radiological orientation. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

head, traumatic brain injury (TBI) or chronic traumatic encephalopathy (CTE) can be caused by martial arts (McKee et al., 2009; Shin et al., 2014; Zhang et al., 2003), especially when not protected (Tiernan et al., 2020). Such injuries may cause microstructural changes in brain cells, which may be manifested as increased diffusivity on DTI. Alternatively, repair processes may occur in the brain after injury, which could also affect the diffusivity. All MRI data in this study were evaluated by a neuroradiologist, and any pathological findings would have been excluded.

Our findings should be viewed in the context of several limitations. First, while our sample size is moderate and comparable to other studies, better powered samples with strict control for relevant variables of no interest are needed for confirmation. Second, the cross-sectional design limits causal interpretations between WM integrity and aggression. It would be interesting to see if a longitudinal design would show significant effects, e.g. that microstructural changes would diminish or become more pronounced over the course of martial arts experience. Third, self-reported data on aggression carry the risk of response bias. Because long-term training affects brain plasticity in athletes (Yarrow et al., 2009) and brain injuries are common in full-contact sports (Shin et al., 2014), selecting martial artists as a case group requires more individualized information, such as exposure to combat and number of knockouts. The use of additional MRI sequences, such as fluidattenuated inversion recovery (FLAIR) or susceptibility-weighted imaging (SWI), and more detailed cognitive testing may also be useful to rule out, e.g., mild traumatic brain injury without loss of consciousness. Future studies would benefit from selecting an even more homogeneous group of martial artists with high levels of aggressiveness, such as MMA athletes only. WM tracts continue to develop into young adulthood (Lebel and Beaulieu, 2011), so research with broader age range samples is needed to understand WM tract development and aggression. Finally, our findings may not generalize to other populations, including females, adolescents, or clinical populations.

Beyond that, the current study has several strengths. We recruited two healthy community samples differing only in their propensity for aggressive behavior (case-control design). Additionally, we controlled for factors influencing DTI, such as sex (Inano et al., 2011; Koolschijn and Crone, 2013), age (Giorgio et al., 2010), intelligence (Yu et al., 2008), and body weight (Xu et al., 2013). The TBSS method used provides greater specificity of results to specific tracts (Haney-Caron et al., 2014).

Our study is the first to provide evidence for changes in WM microstructural integrity associated with predominantly (physical)

appetitive forms of aggression in a community case-control sample, unaffected by typical confounders in patient/inmate samples. Prospective longitudinal studies with larger cohorts and considering the dimensional nature of aggression are needed to examine the developmental course of aggressive behavior in relation to altered WM microstructure. Understanding the neurobiological underpinnings of aggression requires the study of both inmate/patient and community samples, as they are qualitatively different and may provide unique insights into development. Ultimately, understanding the relationship between altered structural connectivity and aggressiveness may contribute to a deeper understanding of the multifactorial causes of aggression and potentially lead to more effective prevention and treatment strategies.

CRediT authorship contribution statement

Stephanie Seidenbecher: Writing – original draft, Visualization, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. Jörn Kaufmann: Writing – review & editing, Visualization, Software, Methodology, Formal analysis. Maria Schöne: Writing – review & editing, Investigation, Data curation, Conceptualization. Henrik Dobrowolny: Writing – review & editing, Visualization, Software, Formal analysis. Kolja Schiltz: Writing – review & editing, Supervision, Conceptualization. Thomas Frodl: Writing – review & editing, Visualization, Supervision. Johann Steiner: Writing – review & editing, Supervision. Bernhard Bogerts: Writing – review & editing, Supervision, Resources, Conceptualization. Thomas Nickl-Jockschat: Writing – review & editing, Visualization, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Ethics approval

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of the Faculty of Medicine, Otto von Guericke-University Magdeburg (20.12.2016, 08/06).

Consent to participate

Informed consent was obtained from all individual participants included in the study.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nicl.2024.103712.

Data availability

Data available on request from the authors. The data that support the findings of this study are available from the corresponding author upon reasonable request.

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