Schizophrenia Bulletin Open
https://doi.org/10.1093/schizbullopen/sgab026

White Matter Matters: Unraveling Violence in Psychosis and Psychopathy

Natalia Tesli*[,1,2], Jaroslav Rokicki[1,3], Ivan I. Maximov[2,3,4], Christina Bell[1,5], Gabriela Hjell[1,6], Tiril Gurholt[1,2], Thomas Fischer-Vieler[1,7], Nina Bang[8,9], Martin Tesli[2,10], Lars T. Westlye[2,3], Ole A. Andreassen[1,2], Ingrid Melle[1,2,11], Ingrid Agartz[1,12,13], Kirsten Rasmussen[8,9], Ragnhild Johansen[8,9], Christine Friestad[14,15], and Unn K. Haukvik[1,11,14]

[1]Norwegian Centre for Mental Disorders Research (NORMENT), Institute of Clinical Medicine, University of Oslo, Oslo, Norway; [2]Norwegian Centre for Mental Disorders Research (NORMENT), Division of Mental Health and Addiction, Oslo University Hospital, Oslo, Norway; [3]Department of Psychology, University of Oslo, Oslo, Norway; [4]Department of Health and Functioning, Western Norway University of Applied Sciences, Bergen, Norway; [5]Department of Psychiatry, Oslo University Hospital, Oslo, Norway; [6]Department of Psychiatry, Østfold Hospital Trust, Graalum, Norway; [7]Division of Mental Health and Addiction, Vestre Viken Hospital Trust, Drammen, Norway; [8]St.Olavs Hospital, Forensic Research Unit, Brøset, Trondheim, Norway; [9]Norwegian University of Science and Technology (NTNU), department of Psychology and Department of Mental Health, Trondheim, Norway; [10]Department of Mental Disorders, Norwegian Institute of Public Health, Oslo, Norway; [11]Department of Adult Psychiatry, Institute of Clinical Medicine, University of Oslo, Norway; [12]Department of Psychiatric Research, Diakonhjemmet Hospital, Oslo, Norway; [13]Centre for Psychiatry Research, Department of Clinical Neuroscience, Karolinska Institutet & Stockholm Health Care Services, Stockholm County Council, Stockholm, Sweden; [14]Centre of Research and Education in Forensic Psychiatry, Oslo University Hospital, Oslo, Norway; [15]University College of Norwegian Correctional Service, Oslo, Norway

*To whom correspondence should be addressed; Oslo University Hospital, PO Box 4956, Nydalen, 0424 Oslo, Norway; tel: +47-23-02-73-50, fax: +47-23-02-73-33, e-mail: natalia.tesli@medisin.uio.no

Individuals with psychotic disorders have an increased risk of committing acts of violence. Neurobiological support for the extent to which violence in psychosis is driven by psychotic symptoms and/or antisocial traits could have clinical and legal implications. Neuroimaging studies have reported white matter (WM) abnormalities in individuals with psychosis and in those with antisocial traits. However, it is unknown whether WM abnormalities in psychosis patients with a history of violence (violent-PSY) resemble those found in nonviolent psychosis patients (nonviolent PSY), violent nonpsychotic individuals (violent non-PSY), or both. Diffusion tensor imaging scans from 301 males including violent-PSY (*n* = 28), violent non-PSY (*n* = 20), nonviolent PSY (*n* = 58), and healthy controls (HC, *n* = 195) were analyzed with tract-based spatial statistics. Fractional anisotropy (FA), mean, axial and radial (RD) diffusivity were compared between groups. Psychopathic traits in the violent groups were measured with Psychopathy Checklist-revisited (PCL-R). Violent-PSY had globally lower FA and higher RD, compared with nonviolent PSY. Both psychosis groups and violent non-PSY group had widespread disruptions in WM compared with HC. There were no significant WM differences between violent-PSY and violent non-PSY. PCL-R scores did not differ between the violence groups and were associated with higher RD in corpus callosum. Here we demonstrate a widespread pattern of reduced WM integrity in violent-PSY compared with nonviolent PSY. The lack of significant WM and PCL-R differences between the violence groups, together with the positive association between PCL-R and WM deficits in violent-PSY and violent non-PSY may indicate shared neurobiological underpinnings of trait violence.

Key words: aggression/antisocial behavior/schizophrenia/forensic psychiatry

Introduction

Epidemiological studies have shown that individuals with psychotic disorders are at a higher risk of committing violent acts compared with the general population.[1–3] In forensic mental health populations, a significant comorbidity has been found between psychosis and antisocial personality disorder (ASPD) as well as between psychosis and psychopathy.[4–6] ASPD and psychopathy are overlapping though not interchangeable constructs, where ASPD is characterized by antisocial behavior, while psychopathy is dominated by interpersonal-affective traits.[7] Comorbid presentation of psychosis and ASPD may double the risk for violence (odds ratio at 2.1),[8] and one in five homicide offenders with psychosis fulfils criteria for psychopathy.[6] The management

of violent behavior in psychosis as well as personality disorders (ASPD and/or psychopathy) incurs tremendous costs for forensic mental health services.[9] Furthermore, while violence is a multifaceted phenomenon with several known environmental stressors and developmental risk factors,[10–12] little is known about putative shared and distinct structural brain abnormalities in psychotic and nonpsychotic violence. Thus, probing neurobiological underpinnings of trait violence in forensic populations could inform future risk evaluations and aid development of therapeutic targets in high-cost mental health services.

Violent offenders with psychosis (violent-PSY) may constitute a subgroup of psychotic disorders characterized by distinctive profiles of neuroanatomical abnormalities,[13,14] yet structural and functional brain imaging studies of violence in psychosis show mixed results.[15] Diffusion weighted MRI has proved to be a promising tool for investigating structural connectivity as well as microstructural properties of the brain. Nonetheless, few studies have explored associations between structural integrity of white matter (WM) and violence/aggression in psychosis. Among psychosis patients, higher levels of aggressive attitudes[16] and impulsivity[17] have been associated with lower WM integrity in the frontal regions. However, a recent study from our group showed no significant differences on any diffusion tensor imaging (DTI) metric between violent and nonviolent PSY.[18] In ASPD/psychopathy, the majority of DTI-studies have been limited to the uncinate fasciculus[19–21]—a WM tract connecting ventral frontal cortex with the temporal lobe[22] and which has previously been linked to a range of cognitive and psychopathological traits in normally developing children and adolescents, including features of psychosis and conduct disorder (i.e. the precursor to ASPD).[23] Two recent systematic reviews of antisocial[24] and psychopathic traits[25] in adults have demonstrated widespread WM microstructural tract impairments not only in the uncinate fasciculus, but also across major association, thalamic, projection and commissural pathways.

WM abnormalities in violent-PSY and ASPD/psychopathy have not been concurrently investigated with DTI. However, studies using other MRI modalities have shown shared whole brain volume reductions,[26] volumetric deficits in hippocampal and parahippocampal regions,[27] lower volumes in anterior cingulate cortex[28] as well as thinner medial frontal cortex[29] with an exception of one study which did not find any shared structural abnormalities.[30] Based on the results from previous DTI studies, hypothetical shared neurobiological underpinnings for violence in antisocial and psychotic individuals may arise from disrupted connections between brain regions implicated in a plethora of cognitive and affective functions including impulse control, emotion and reward processing.[31–33] Thus, a thorough investigation of whole-brain structural connectivity in psychotic and nonpsychotic violence is needed to identify shared and/or distinct disruptions in WM circuitry.

The current study aimed at identifying neuroimaging correlates of psychotic and nonpsychotic violence using DTI and tract-based spatial statistics (TBSS)[34] with multiple diffusion tensor measures. Firstly, we explored WM microstructural differences between the four groups (violent-PSY, nonviolent-PSY, violent non-PSY and healthy controls (HC)). Secondly, we studied possible associations between psychopathy traits in violent-PSY and violent non-PSY and WM integrity. We hypothesized that (1) both psychosis groups would have widespread WM disruptions compared with HC and (2) that we would find more widespread disruptions in violent-PSY than nonviolent PSY. Due to the clinical overlap between violent-PSY and violent non-PSY we hypothesized (3) that these groups would show similar pattern of WM microstructural abnormalities, with more pronounced abnormalities in violent-PSY. Finally, we hypothesized that psychopathic traits would show negative associations with DTI-based proxies for WM integrity.

Methods

Sample

The sample (n = 301) consisted of four groups of male participants. The inclusion was restricted to male gender due to low number of females in the violent-PSY and violent non-PSY group. All diagnoses were based on the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV).

The violent offenders with psychosis (violent-PSY, n = 28) group consisted of patients primarily with DSM-IV diagnoses in the schizophrenia spectrum (n = 27) or psychosis NOS (n = 1), recruited from high-security forensic psychiatric wards in the Oslo region, Norway. Inclusion criteria for this group were murder, attempted murder as well as severe physical assaults towards other people according to the MacArthur criteria.[35] The subjects from the nonviolent psychosis (nonviolent PSY, n = 58) group were recruited from major psychiatric hospitals and their outpatient clinics in Oslo, Norway, and had matching DSM-IV diagnoses in the schizophrenia spectrum (n = 57) or psychosis NOS (n = 1). The group of violent offenders without psychosis (non-PSY violent, n = 20) consisted of incarcerated persons serving a preventive detention sentence (Oslo region, Norway) due to perpetration of a violent crime (complying with the MacArthur criteria[35]). Preventive detention is a sanction imposed in cases of particularly severe crimes involving interpersonal violence. The sanction can be prolonged as long as the offender is considered to constitute a risk to others, which in theory may involve a life-long imprisonment. As of 2020, a total of 119 persons served a preventive detention sentence in Norway. The nonviolent nonpsychotic

healthy control group (HC, n = 195) was randomly selected from the Norwegian national population registry (https://www.ssb.no/en) and invited to participate. All participants were drawn from the ongoing multicenter Thematically Organized Psychosis project at the University of Oslo, Norway. Inclusion criteria for all four groups were age between 18 and 65 years, IQ score above 65, no head trauma leading to loss of consciousness and absence of previous or current somatic illness that might have affected brain morphology. In total, 56 subjects were included in our previous DTI-study in schizophrenia patients with a history of violence.[18]

The study was approved by the Norwegian Regional Committee for Medical Research Ethics, the Norwegian Data Inspectorate and relevant correctional agencies. Written informed consent was obtained from all participants after complete description of the study.

Clinical Assessment

Trained physicians, psychiatrists and clinical psychologists assessed each participant, with thorough clinical examination. DSM-IV diagnoses for violent-PSY and nonviolent PSY were confirmed with SCID-1.[36] Both PSY groups had their level of psychosocial functioning evaluated with the Global Assessment of Function (GAF) scale. Current psychotic symptoms were rated with the Positive and Negative Syndrome Scale (PANSS).[37] Medication use was assessed and Defined Daily Dosages (DDD) of antipsychotic medication use were calculated in accordance with the guidelines from World Health Organization (https://www. whocc.no/atc_ddd_index/).

The assessment of violence for violent-PSY and violent non-PSY was based on court files and hospital records. Psychopathy traits were screened with the Psychopathy Checklist-revisited (PCL-R).[38] The PCL-R applies a 20-item scale to measure personality traits and behaviors related to the construct of psychopathy in research and forensic settings. In our study the evaluation procedure was based on a thorough interview as well as review of the individual´s history of violent offending including court documentation and/or medical records.

To ensure no previous history of violence in the nonviolent PSY group, their medical files have been thoroughly examined. This procedure entailed evaluation of all study inclusion protocols, which are based on detailed information obtained from medical records including clinical journals and structured interview with the patient.

HC were screened with the Primary Care Evaluation of Mental Disorders (Prime-MD)[39] questionnaire and interviewed to confirm no history of psychiatric disorder.

IQ was measured in all subjects with the Norwegian version of the Wechsler Abbreviated Scale of Intelligence (WASI-II)[40] by trained psychologists.

MRI Acquisition

MRI data were collected on a 3T GE 750 Discovery scanner using a 32-channel head coil at Oslo University Hospital (supplementary methods).

Diffusion Data Postprocessing and Quality Control

We applied an optimized postprocessing pipeline of diffusion-weighted MRI data, described in detail by Maximov et al[41] and performed a quality control procedure of diffusion data (supplementary methods).

Statistical Analyses

Clinical and Demographic Characteristics. Descriptive statistical analyses were performed in R (version 3.5.3). The analysis of variance or t-test were applied to assess group differences on age, psychometric measures, use of medication and IQ. All statistical tests were two tailed with statistical significance reported at the 0.05 level.

Tract-based Spatial Statistics. Voxelwise analysis of diffusion metrics (fractional anisotropy (FA), mean diffusivity (MD), radial diffusivity (RD), axial diffusivity (AD)) was performed with TBSS[34] (supplementary methods). The obtained single-subject images for each metric were fed into voxelwise between-subject statistics performed with nonparametric permutation-based inference testing implemented in FSL's PALM tool.[42] Main effects of group (violent-PSY, violent non-PSY, nonviolent PSY, and HC) on diffusion metrics (FA, MD, AD, and RD) were tested using a general linear model (GLM) by creating pairwise contrasts with corresponding F-tests and covarying for age. The effects of medication were tested by including DDD of current antipsychotics as a covariate in the linear regression model among psychosis groups. Associations of psychopathy traits on DTI-metrics were analyzed with a linear regression model with PCL-R as a continuous variable among violent groups covarying for age and psychosis.

Threshold-free cluster enhancement (TFCE)[43] was used to avoid arbitrarily defining the cluster-forming threshold. The voxelwise maps were thresholded at $P <$ .05, correcting for multiple comparisons across modalities and contrasts (family-wise error [FWE]-corrected)[44,45] for all the analyses except for the analyses with PCL-R which were corrected across voxels within each contrast (due to low number of PCL-R scores). Anatomical localizations of significant clusters showing between group differences were determined with the atlas tool provided by FSL (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/Atlases).

Additionally, we computed mean values for each DTI-metric (FA, MD, AD, RD) averaged over the TBSS skeletons for all 301 subjects (supplementary figure S1). As low IQ is a risk factor for violent behaviour,[46] the mean values of each metric for each subject were fed into

regression models with IQ and age as covariates to test whether IQ contributes significantly to the models.

Probabilistic Tractography. To further investigate the putative WM disruptions in connectivity patterns for significant pairwise differences in diffusion metrics we performed a probabilistic tractography analysis. First, we created a binary mask based on TBSS results by binarizing voxels at the $P < .05$ FWE-corrected. Next, the mask was fed into the probabilistic tractography algorithm as a seed region. Briefly, the probabilistic tractography was executed as a three-step process. First, diffusion data was used to calculate the fiber orientations and their uncertainty in each voxel for each subject with bedpostX implemented in FMRIB's Diffusion Toolbox (FDT).[47] Then, the seed mask prepared in MNI space was transformed into diffusion space for each subject using inverted transformation from the TBSS registration stage. Next, path probability maps were computed in the diffusion space with the default parameters using PROBTRACKX2.[47,48] Finally, probabilistic tractography maps for all subjects were transformed back into the MNI space and submitted to PALM for statistical significance testing with a GLM. The statistical maps were FWE-corrected at $P < .05$ for multiple comparisons.

Results

Clinical and Demographic Characteristics

Briefly, there was a significant main effect of group on age at MRI ($F_{3,297} = 6.95$, $P < .001$, IQ ($F_{3,265} = 51.26$, $P < .001$) and PANSS for all subscales (PANSS positive subscale $F_{2,101} = 11.03$, $P < .001$; PANSS negative subscale $F_{2,101} = 17.92$, $P < .001$; PANSS general subscale $F_{2,101} = 15.45$, $P < .001$, post-hoc pairwise comparisons in supplementary table S1). Additionally, violent-PSY had significantly lower GAF scores (GAF-S $t_{69} = 2.38$, $P < .01$; GAF-F $t_{66} = 2.95$, $P < .004$) and higher use of antipsychotic medication ($t_{50} = -2.24$, $P < .02$) compared with nonviolent PSY. There were no other significant differences for other demographic or clinical variables (table 1).

White Matter Tract Differences Between Groups

There was a significant main effect of groups on all 4 DTI-metrics (figure 1), with global group differences on FA, MD and RD, together with more circumscribed differences on AD. Pairwise comparisons (figure 2, supplementary table S2) revealed widespread FA reductions in the violent-PSY group compared with nonviolent PSY (including bilateral anterior thalamic radiation (ATR), corticospinal tract (CST), cingulum bundle (CG), inferior fronto-occipital fasciculus (IFOF), inferior longitudinal fasciculus (ILF), superior longitudinal fasciculus (SLF), uncinate fasciculus (UF) as well as corpus callosum (CC),

Table 1. Demographic and Clinical Characteristics

	Violent-PSY		Nonviolent PSY		Violent non-PSY		HC		
	n =28		*n* =58		*n* =20		*n* = 195		
	Mean (SD)	Range	Mean (SD)	Range	Mean (SD)	Range	Mean (SD)	Range	*F*-test
Age at MR	34.96 (9.19)	21.45–57.56	31 (8.98)	19.04–54.48	40.33 (13.47)	22.74–65.91	36.68 (9.33)	18.37–56.4	$P < .0001$
IQ	91.56 (14.45)	67–113	100.11 (14.51)	69–127	98.69 (11.55)	82–121	115.64 (9.3)	76–134	$P < .0001$
PANSS positive	15.88 (7.29)	7–35	14.45 (4.98)	7–28	8.7 (3.73)	7–23			$P < .0001$
PANSS negative	17.42 (6.65)	7–31	17.4 (6.52)	7–32	8.5 (2.06)	7–14			$P < .0001$
PANSS general	30.73 (8.37)	20–54	32.98 (8.57)	17–54	21.2 (6.67)	16–39			$P < .0001$
									***t*-test**
GAF symptom	41.78 (8.92)	25–66	47.48 (12.66)	28–85					$P < .01$
GAF function	39.26 (9.34)	20–63	46.5 (12.46)	27–85					$P < .004$
Age at psychosis onset	24.35 (7.36)	14–43	23.45 (6.16)	15–52					NS
Age at first admission	24.11 (6.42)	16–45	25.33 (6.53)	16–52					NS
Antipsychotics (DDD)	1.82 (0.83)	0.63–3.45	1.37 (0.82)	0.25–3.58					$P < .02$
PCL-R	20.72 (7.61)	4–30			21.17 (8.27)	10–35			NS

Abbreviations: violent-PSY, violent offenders with psychosis; nonviolent PSY, nonviolent patients with psychosis; violent non-PSY, nonpsychotic violent offenders; HC, healthy controls; SD, standard deviation; PANSS Positive and Negative Syndrome Scale; GAF, Global Assessment of Function split version; DDD, defined daily doses; PCL-R, Psychopathy Checklist-Revised; NS, nonsignificant results.

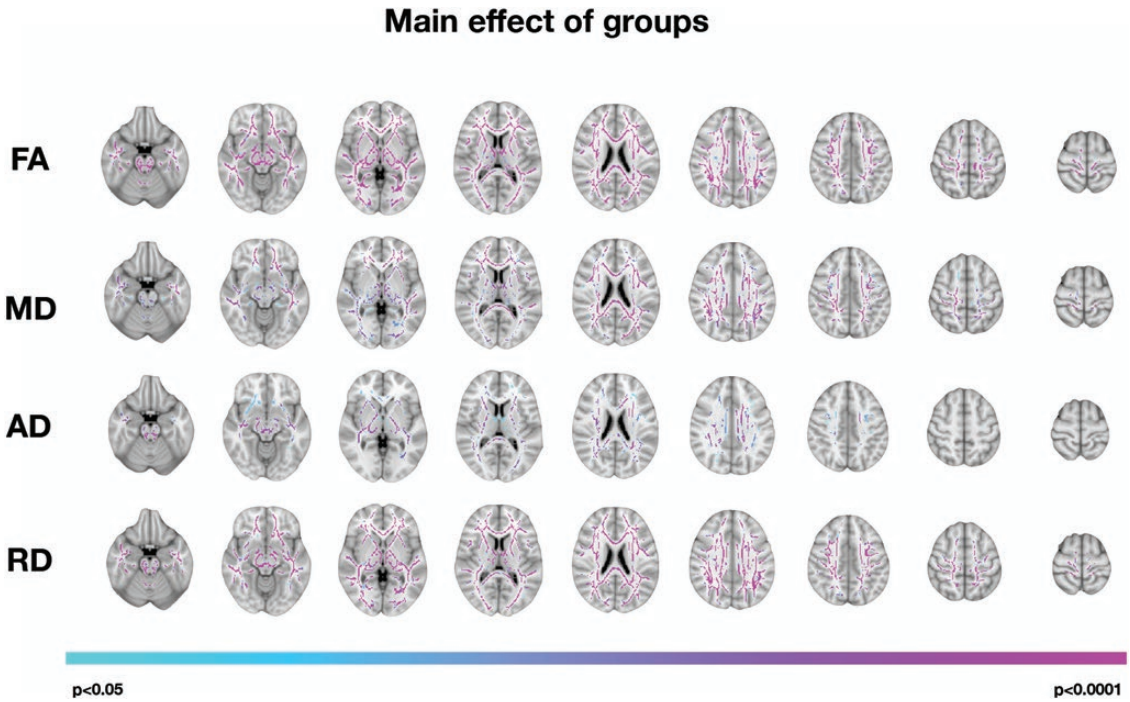

Fig. 1. Results from the TBSS analysis and permutation testing thresholded at $P < .05$ (FWE-corrected across modalities) using threshold-free cluster enhancement. Statistical maps show main effect of groups on 4 DTI-metrics. FA, fractional anisotropy; MD, mean diffusivity; AD, axial diffusivity; RD, radial diffusivity.

forceps major and minor. The violent-PSY group also had higher RD in multiple WM tracts (including bilateral ATR, CST, CG, IFOF, ILF, SLF, UF as well as CC, forceps minor and major) compared with nonviolent PSY. Further, violent non-PSY and violent-PSY groups had global reductions in FA compared with HC comprising all major WM tracts. Next, both PSY groups had higher MD and RD compared with HC. The differences in MD encompassing major association, commissural and projection tracts were more global in violent-PSY and more circumscribed in nonviolent PSY (including bilateral ATR, IFOF, ILF and SLF). A similar pattern was present for RD, with higher RD in the majority of WM tracts for violent-PSY and higher RD focally in more circumscribed clusters in nonviolent PSY (including left SLF, bilateral CST, ATR, and IFOF). Higher RD was also observed in the majority of WM tracts within the TBSS skeleton in violent non-PSY compared with HC. Further, violent non-PSY had focally lower FA and AD compared with nonviolent PSY. There were no differences between violent-PSY and violent non-PSY on any DTI-metric. There were no significant effects of antipsychotic medication on any DTI-metric. The additional regression analyses on mean values of DTI-metrics showed that IQ did not significantly contribute to the models (data not shown).

The PCL-R analyses in the violence groups (figure 3) showed a significant positive association between PCL-R and RD in one cluster encompassing the body and splenium of CC.

The probabilistic streamline tracking was seeded from the local maxima cluster with abnormal FA from the comparison between violent-PSY and nonviolent PSY and comprised 11 voxels located in the midbrain and included left superior cerebellar peduncle. The tractography results revealed significantly disrupted streamlines in violent-PSY passing through the following WM tracts: the left ATR including the anterior limb of the internal capsule adjacent to the nucleus accumbens and approaching the ventral prefrontal cortex, left posterior limb of the internal capsule including corticospinal tract, posterior fibers of fornix at the level of mamillary bodies, as well as the left middle and inferior cerebellar peduncle (figure 4).

Discussion

The main findings in the current study were brain-wide WM disruptions in the violent compared with nonviolent PSY group but no significant WM microstructural differences between the violent-PSY and violent non-PSY group. Further, both psychosis groups and violent non-PSY group had widespread WM abnormalities compared with HC. While previous DTI studies have documented widely distributed case-control differences between patients with schizophrenia and HC,[49,50] this is to the best of our knowledge the first study that demonstrated a widespread pattern of reduced WM integrity in violent-PSY compared with nonviolent PSY utilizing multiple DTI-metrics and additional probabilistic tractography.

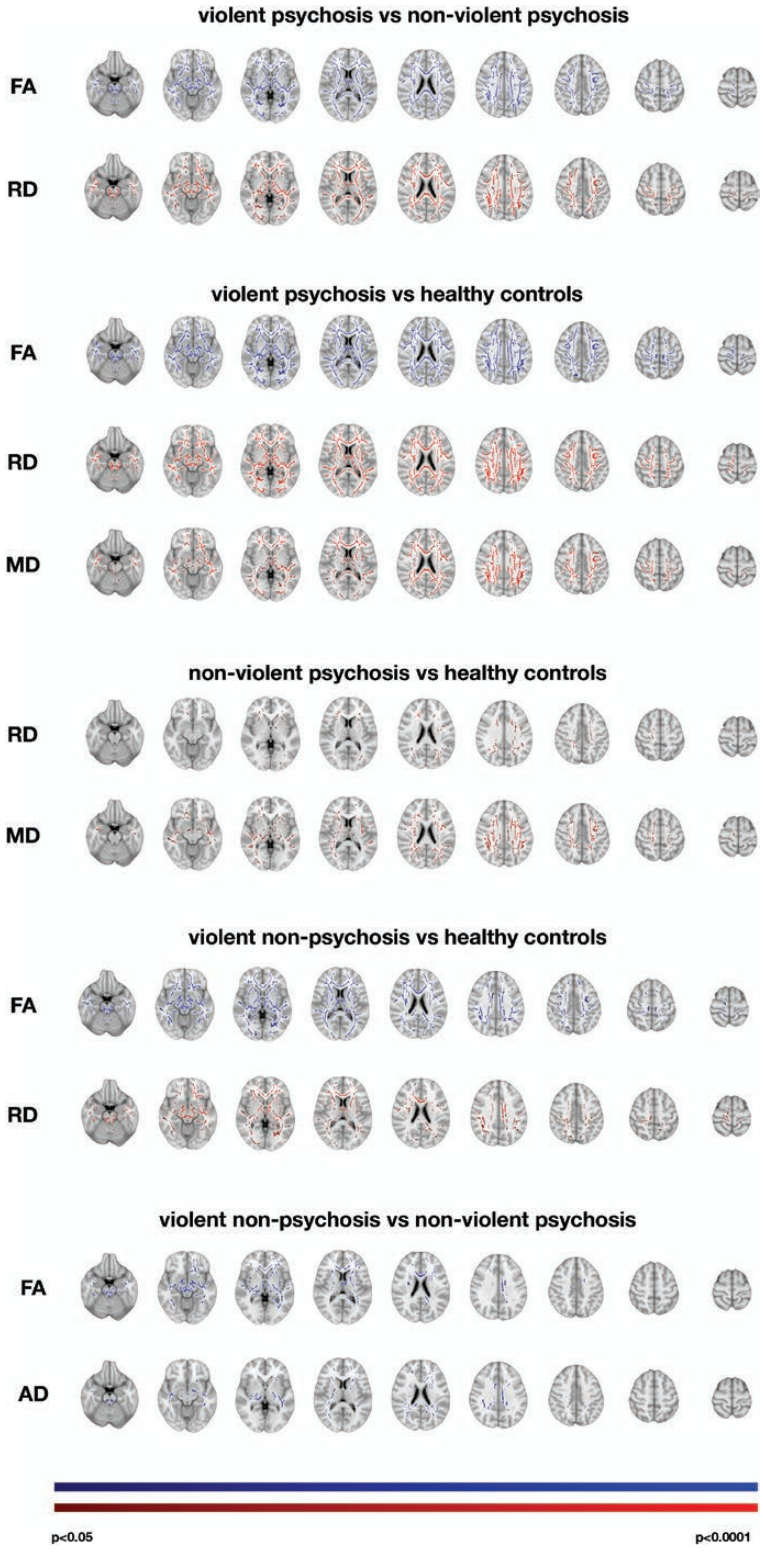

Fig. 2. Results from the TBSS analysis and permutation testing thresholded at $P < .05$ (FWE-corrected across modalities and contrasts) using threshold-free cluster enhancement. Statistical maps show significantly increased (red) and decreased (blue) DTI-metrics for pairwise comparisons between the groups. FA, fractional anisotropy; MD, mean diffusivity; AD, axial diffusivity; RD, radial diffusivity.

The widespread abnormalities indicated by lower FA and higher RD in violent-PSY compared with nonviolent PSY may suggest a global breakdown in the inter-regional communication between higher-order cortical regions involved in a plethora of cognitive and emotion regulatory functions. Indeed, the structural disruptions in

violent-PSY overlap with large-scale functional networks associated with saliency mapping, inhibitory control as well as moral decision-making which have been associated with aberrant connectivity patterns in individuals with antisocial behavior and/or psychopathic traits.[51–54] A recent study reported FA reductions associated with callous-unemotional traits (a core affective component of psychopathy) in several tracts corresponding to large-scale networks including the default mode, central executive and salience network.[33] Additionally, aberrant communication between the hubs of these functional networks has been linked to affective and interpersonal symptoms of psychopathy in a large forensic sample.[55] It should, however, be emphasized that psychosis per se is not sufficient for the putative neurobiological profile underlying violent behavior.

The observed differences between the psychosis groups were not limited to FA, which is highly sensitive to microstructural properties although lacks specificity to the type of these changes (e.g. axonal diameter, fiber density, myelination, crossing fibers),[56,57] but were also present for RD which has been shown to correlate with abnormal processes involved in de- and dysmyelination.[58]

When we interrogated the differences between the psychosis groups in more depth with probabilistic tractography seeded from the voxels located in the midbrain, we found disrupted WM tracts in the violent-PSY extending towards the striatal and ventral prefrontal regions. Among the affected fibers were anterior (ALIC) and posterior (PLIC) limbs of the internal capsule. The ALIC separates the caudate nucleus and the putamen in the dorsal striatum, a brain region implicated in decision-making through the integration of emotionally and motivationally salient stimuli.[59] FA in the caudate nucleus has been shown to be negatively correlated with motor impulsivity in schizophrenia,[17] and structural disruptions (reduced AD) in ALIC and PLIC have previously been reported in offenders diagnosed with ASPD.[60] Further, structural abnormalities within the striato-thalamo-frontal circuitry have been associated with the antisocial/affective component of PCL-R in male psychopathic offenders.[32] It has been hypothesized that impairments in the striatum in antisocial individuals may lead to inability of response termination to a stimulus that is no longer rewarding and reduced flexibility to use contextual information, which may exacerbate impulsivity and aggressive behaviour.[61]

The PCL-R scores did not differ significantly between the violent-PSY and violent non-PSY, and were associated with WM microstructural abnormalities in the left body/splenium of CC across the violence groups. The CC is essential to interhemispheric communication,[62] involved in sensory-motor integration,[63] and approach/withdrawal-related behavior associated with aggression in forensic samples as well as in community populations.[64] We found a positive correlation between the RD in the CC and PCL-R scores which may indicate disruptions in the approach-motivation circuitry linked with antisocial

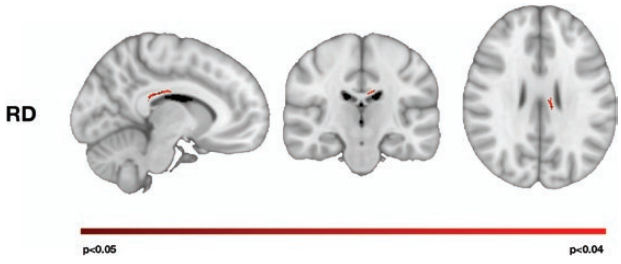

Fig. 3. Results from the TBSS analyses and permutation testing thresholded at $P < .05$ (FWE-corrected) using threshold-free cluster enhancement. Statistical maps show positive association between RD and PCL-R in violence groups covaried for psychosis and age. PCL-R, Psychopathy Checklist-revisited; RD, radial diffusivity.

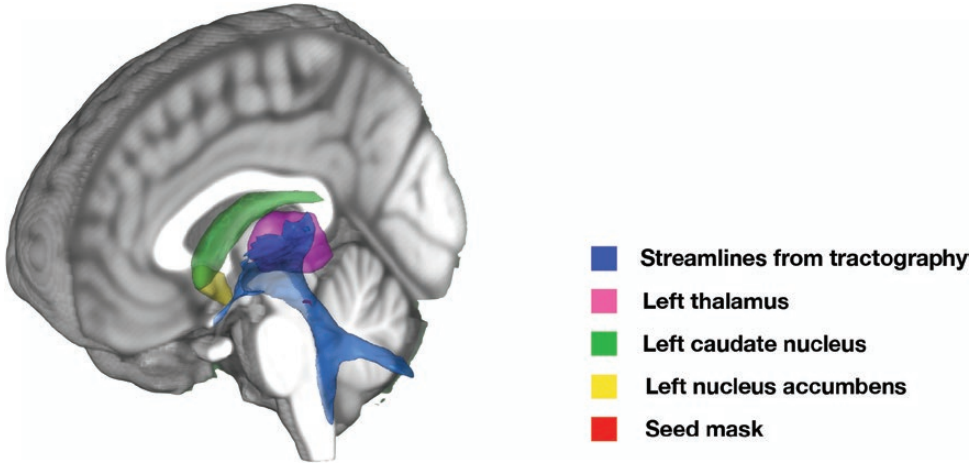

Fig. 4. Results from probabilistic tractography using seed voxels from the comparison between the violent-PSY and nonviolent PSY. Statistical maps thresholded at $P < .05$ (FWE-corrected) show significantly disrupted streamlines in violent-PSY (blue). For illustrative purposes seed mask is shown in red, thalamus in magenta, caudate nucleus in green and nucleus accumbens in yellow.

behavior. Associations between deficits in WM integrity of CC and PCL-R have been previously reported in individuals diagnosed with ASPD.[65] These associations were shown for FA, while our results were confined to RD, possibly implying progressive axonal damage due to increased myelin degradation.[66]

The lack of significant WM microstructural and PCL-R differences between the violence groups, together with the positive association between PCL-R and WM deficits in violent-PSY and violent non-PSY may indicate shared neurobiological underpinnings of trait violence and are in line with the existing literature on overlapping neuropsychological and emotion processing deficits in violent individuals with psychosis and ASPD/psychopathy[67,68] as well as with previous reports indicating shared structural abnormalities in violent individuals with or without psychosis.[26–29]

This study has certain limitations. The number of subjects in the violence groups was relatively small which reflects challenges related to recruitment and assessment of individuals from high-security forensic wards and prisons. Nonetheless, the violent-PSY sample matches the two other studies investigating correlates of impulsivity/aggression in schizophrenia patients (n = 14–25).[16,17] Due to low number of datapoints for PCL-R we applied a less conservative approach to multiple-comparison correction compared with the main analyses (FWE-correction within each contrast). Hence, these findings should be interpreted with caution. The observed associations between WM microstructure and PCL-R were confined to CC, thus it suggests that the PCL-R construct does not exhaustively capture the affective and cognitive disturbances in violent behavior. While we controlled for known confounders such as IQ and medication, we did not control for illicit substance use or alcohol use as individuals in both violence groups were institutionalized at the time of inclusion in the study and were not supposed to have access to illicit substances or alcohol. We cannot exclude the possibility that earlier substance abuse may have affected the results taking into account high comorbidity between psychosis, ASPD and substance use disorders.[69,70] Additionally, previous brain imaging research has suggested that myelination may be affected by antipsychotic medication[71] and the violent-PSY group had a significantly higher total DDD of antipsychotic medication use compared with nonviolent PSY group. However, this is less likely as our supplementary analyses in the psychosis groups showed that the results were unaffected by the cumulative medication load. Further, we cannot exclude the possibility that the observed WM microstructural deficits in the violent-PSY and violent non-PSY are caused by a shared cumulative load of other factors than trait violence/aggression, for example, similar neurocognitive profiles.

Among the strengths of our study is the implementation of an optimized postprocessing pipeline for diffusion data[41] and application a stringent multiple comparison correction across modalities and contrasts for the main TBSS and tractography analyses.[42,44] A major strength is that all participants were scanned on the same scanner with no upgrades during the study. The violent-PSY group comprised exclusively individuals who committed serious acts of violence, i.e., murder, attempted murder as well as severe physical assault towards other people. The violent non-PSY group was unique for research purposes as it comprised individuals serving preventive detention prison sentence which is the most severe penalty according to Norwegian legislation.

In summary, we report global WM differences between the psychosis patients with and without a history of violence. These differences were further probed with tractography which revealed disrupted structural connectivity in the violent-PSY group in the striatal regions. We did not observe any differences between the psychotic and nonpsychotic persons with a history of violence, and both violence groups had their PCL-scores associated with WM abnormalities in CC. These results corroborate the hypothesis of WM microstructural correlates of violence in psychosis and may suggest shared violence-related structural abnormalities across psychotic and nonpsychotic offenders.

Supplementary Material

Supplementary data are available at *Schizophrenia Bulletin Open* online.

Funding

This work was supported by The Research Council of Norway (OA, #223273, #249795, #298646), KG Jebsen Stiftelsen and South Eastern Norway Health Authorities (UKH, #2016044; UKH, #2019117; UKH, #2020100, OA, #2017112).

Disclosure

The authors report no financial relationships with commercial interest, other than Dr Andreassen who received speaker's honorarium from Lundbeck and Sunovion and is a consultant for HealthLytix.

References

1. Swanson JW, Swartz MS, Van Dorn RA, *et al.* A national study of violent behavior in persons with schizophrenia. *Arch Gen Psychiatry.* 2006;63(5):490–499.
2. Fleischman A, Werbeloff N, Yoffe R, Davidson M, Weiser M. Schizophrenia and violent crime: a population-based study. *Psychol Med.* 2014;44(14):3051–3057.
3. Witt K, Lichtenstein P, Fazel S. Improving risk assessment in schizophrenia: epidemiological investigation of criminal history factors. *Br J Psychiatry.* 2015;206(5):424–430.

4. Putkonen A, Kotilainen I, Joyal CC, Tiihonen J. Comorbid personality disorders and substance use disorders of mentally ill homicide offenders: a structured clinical study on dual and triple diagnoses. *Schizophr Bull.* 2004;30(1):59–72.
5. Maghsoodloo S, Ghodousi A, Karimzadeh T. The relationship of antisocial personality disorder and history of conduct disorder with crime incidence in schizophrenia. *J Res Med Sci.* 2012;17(6):566–571.
6. Laajasalo T, Salenius S, Lindberg N, Repo-Tiihonen E, Häkkänen-Nyholm H. Psychopathic traits in Finnish homicide offenders with schizophrenia. *Int J Law Psychiatry.* 2011;34(5):324–330.
7. Werner KB, Few LR, Bucholz KK. Epidemiology, comorbidity, and behavioral genetics of antisocial personality disorder and psychopathy. *Psychiatr Ann.* 2015;45(4):195–199.
8. Witt K, van Dorn R, Fazel S. Risk factors for violence in psychosis: systematic review and meta-regression analysis of 110 studies. *PLoS One.* 2013;8(2):e55942.
9. Wilson S, James D, Forrester A. The medium-secure project and criminal justice mental health. *Lancet.* 2011;378(9786):110–111.
10. Anderson NE, Kiehl KA. Psychopathy and aggression: when paralimbic dysfunction leads to violence. *Curr Top Behav Neurosci.* 2014;17:369–393.
11. Fazel S, Wolf A, Palm C, Lichtenstein P. Violent crime, suicide, and premature mortality in patients with schizophrenia and related disorders: a 38-year total population study in Sweden. *Lancet Psychiatry.* 2014;1(1):44–54.
12. Oakley C, Harris S, Fahy T, Murphy D, Picchioni M. Childhood adversity and conduct disorder: a developmental pathway to violence in schizophrenia. *Schizophr Res.* 2016;172(1-3):54–59.
13. Widmayer S, Sowislo JF, Jungfer HA, *et al.* Structural magnetic resonance imaging correlates of aggression in psychosis: a systematic review and effect size analysis. *Front Psychiatry.* 2018;9:217.
14. Schiffer B, Leygraf N, Müller BW, *et al.* Structural brain alterations associated with schizophrenia preceded by conduct disorder: a common and distinct subtype of schizophrenia? *Schizophr Bull.* 2013;39(5):1115–1128.
15. Fjellvang M, Grøning L, Haukvik UK. Imaging violence in schizophrenia: a systematic review and critical discussion of the MRI literature. *Front Psychiatry.* 2018;9:333.
16. Hoptman MJ, Volavka J, Johnson G, Weiss E, Bilder RM, Lim KO. Frontal white matter microstructure, aggression, and impulsivity in men with schizophrenia: a preliminary study. *Biol Psychiatry.* 2002;52(1):9–14.
17. Hoptman MJ, Ardekani BA, Butler PD, Nierenberg J, Javitt DC, Lim KO. DTI and impulsivity in schizophrenia: a first voxelwise correlational analysis. *Neuroreport.* 2004;15(16):2467–2470.
18. Tesli N, Westlye LT, Storvestre GB, *et al.* White matter microstructure in schizophrenia patients with a history of violence. *Eur Arch Psychiatry Clin Neurosci.* 2019;271(4):623–634.
19. Wolf RC, Pujara MS, Motzkin JC, *et al.* Interpersonal traits of psychopathy linked to reduced integrity of the uncinate fasciculus. *Hum Brain Mapp.* 2015;36(10):4202–4209.
20. Craig MC, Catani M, Deeley Q, *et al.* Altered connections on the road to psychopathy. *Mol Psychiatry*. 2009;14(10):946–953, 907.
21. Sobhani M, Baker L, Martins B, Tuvblad C, Aziz-Zadeh L. Psychopathic traits modulate microstructural integrity of right uncinate fasciculus in a community population. *Neuroimage Clin.* 2015;8:32–38.
22. Leng B, Han S, Bao Y, *et al.* The uncinate fasciculus as observed using diffusion spectrum imaging in the human brain. *Neuroradiology.* 2016;58(6):595–606.
23. Alnæs D, Kaufmann T, Doan NT, *et al.* Association of heritable cognitive ability and psychopathology with white matter properties in children and adolescents. *JAMA Psychiatry.* 2018;75(3):287–295.
24. Waller R, Dotterer HL, Murray L, Maxwell AM, Hyde LW. White-matter tract abnormalities and antisocial behavior: a systematic review of diffusion tensor imaging studies across development. *Neuroimage Clin.* 2017;14:201–215.
25. Pujol J, Harrison BJ, Contreras-Rodriguez O, Cardoner N. The contribution of brain imaging to the understanding of psychopathy. *Psychol Med.* 2019;49(1):20–31.
26. Barkataki I, Kumari V, Das M, Taylor P, Sharma T. Volumetric structural brain abnormalities in men with schizophrenia or antisocial personality disorder. *Behav Brain Res.* 2006;169(2):239–247.
27. Yang Y, Raine A, Han CB, Schug RA, Toga AW, Narr KL. Reduced hippocampal and parahippocampal volumes in murderers with schizophrenia. *Psychiatry Res.* 2010;182(1):9–13.
28. Kumari V, Uddin S, Premkumar P, *et al.* Lower anterior cingulate volume in seriously violent men with antisocial personality disorder or schizophrenia and a history of childhood abuse. *Aust N Z J Psychiatry.* 2014;48(2):153–161.
29. Narayan VM, Narr KL, Kumari V, *et al.* Regional cortical thinning in subjects with violent antisocial personality disorder or schizophrenia. *Am J Psychiatry.* 2007;164(9):1418–1427.
30. Del Bene VA, Foxe JJ, Ross LA, Krakowski MI, Czobor P, De Sanctis P. Neuroanatomical abnormalities in violent individuals with and without a diagnosis of schizophrenia. *PLoS One.* 2016;11(12):e0168100.
31. Kiehl KA, Smith AM, Hare RD, *et al.* Limbic abnormalities in affective processing by criminal psychopaths as revealed by functional magnetic resonance imaging. *Biol Psychiatry.* 2001;50(9):677–684.
32. Hoppenbrouwers SS, Nazeri A, de Jesus DR, *et al.* White matter deficits in psychopathic offenders and correlation with factor structure. *PLoS One.* 2013;8(8):e72375.
33. Dotterer HL, Waller R, Shaw DS, *et al.* Antisocial behavior with callous-unemotional traits is associated with widespread disruptions to white matter structural connectivity among low-income, urban males. *Neuroimage Clin.* 2019;23:101836.
34. Smith SM, Jenkinson M, Johansen-Berg H, *et al.* Tract-based spatial statistics: voxelwise analysis of multi-subject diffusion data. *Neuroimage.* 2006;31(4):1487–1505.
35. Monahan J, Steadman HJ, Appelbaum PS, *et al.* Developing a clinically useful actuarial tool for assessing violence risk. *Br J Psychiatry.* 2000;176:312–319.
36. Spitzer RL, Williams JB, Gibbon M, First MB. The structured clinical interview for DSM-III-R (SCID). I: history, rationale, and description. *Arch Gen Psychiatry.* 1992;49(8):624–629.
37. Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophr Bull.* 1987;13(2):261–276.
38. Hare RD. *The Hare Psychopathy Checklist Revisited (Hare PCL-R).* Toronto: Multi-Health Systems, Incorporated; 2003.
39. Spitzer RL, Williams JB, Kroenke K, *et al.* Utility of a new procedure for diagnosing mental disorders in primary care. The PRIME-MD 1000 study. *JAMA.* 1994;272(22):1749–1756.

40. Hays JR, Reas DL, Shaw JB. Concurrent validity of the Wechsler abbreviated scale of intelligence and the Kaufman brief intelligence test among psychiatric inpatients. *Psychol Rep.* 2002;90(2):355–359.
41. Maximov II, Alnaes D, Westlye LT. Towards an optimised processing pipeline for diffusion magnetic resonance imaging data: Effects of artefact corrections on diffusion metrics and their age associations in UK Biobank. *Hum Brain Mapp.* 2019;40(14):4146–4162.
42. Winkler AM, Ridgway GR, Webster MA, Smith SM, Nichols TE. Permutation inference for the general linear model. *Neuroimage.* 2014;92:381–397.
43. Smith SM, Nichols TE. Threshold-free cluster enhancement: addressing problems of smoothing, threshold dependence and localisation in cluster inference. *Neuroimage.* 2009;44(1):83–98.
44. Alberton BAV, Nichols TE, Gamba HR, Winkler AM. Multiple testing correction over contrasts for brain imaging. *Neuroimage.* 2020;216:116760.
45. Winkler AM, Webster MA, Brooks JC, Tracey I, Smith SM, Nichols TE. Non-parametric combination and related permutation tests for neuroimaging. *Hum Brain Mapp.* 2016;37(4):1486–1511.
46. Jacob L, Haro JM, Koyanagi A. Association between intelligence quotient and violence perpetration in the English general population. *Psychol Med.* 2019;49(8):1316–1323.
47. Behrens TE, Berg HJ, Jbabdi S, Rushworth MF, Woolrich MW. Probabilistic diffusion tractography with multiple fibre orientations: What can we gain? *Neuroimage.* 2007;34(1):144–155.
48. Behrens TE, Woolrich MW, Jenkinson M, *et al.* Characterization and propagation of uncertainty in diffusion-weighted MR imaging. *Magn Reson Med.* 2003;50(5):1077–1088.
49. Kelly S, Jahanshad N, Zalesky A, *et al.* Widespread white matter microstructural differences in schizophrenia across 4322 individuals: results from the ENIGMA Schizophrenia DTI Working Group. *Mol Psychiatry.* 2018;23(5):1261–1269.
50. Tønnesen S, Kaufmann T, Doan NT, *et al.* White matter aberrations and age-related trajectories in patients with schizophrenia and bipolar disorder revealed by diffusion tensor imaging. *Sci Rep.* 2018;8(1):14129.
51. Sethi A, Gregory S, Dell'Acqua F, *et al.* Emotional detachment in psychopathy: Involvement of dorsal default-mode connections. *Cortex.* 2015;62:11–19.
52. Yoder KJ, Harenski C, Kiehl KA, Decety J. Neural networks underlying implicit and explicit moral evaluations in psychopathy. *Transl Psychiatry.* 2015;5:e625.
53. Deming P, Koenigs M. Functional neural correlates of psychopathy: a meta-analysis of MRI data. *Transl Psychiatry.* 2020;10(1):133.
54. Jiang W, Shi F, Liao J, *et al.* Disrupted functional connectome in antisocial personality disorder. *Brain Imaging Behav.* 2017;11(4):1071–1084.
55. Espinoza FA, Vergara VM, Reyes D, *et al.* Aberrant functional network connectivity in psychopathy from a large (N = 985) forensic sample. *Hum Brain Mapp.* 2018;39(6):2624–2634.
56. Alexander AL, Lee JE, Lazar M, Field AS. Diffusion tensor imaging of the brain. *Neurotherapeutics.* 2007;4(3):316–329.
57. Novikov DS, Kiselev VG, Jespersen SN. On modeling. *Magn Reson Med.* 2018;79(6):3172–3193.
58. Song SK, Sun SW, Ramsbottom MJ, Chang C, Russell J, Cross AH. Dysmyelination revealed through MRI as increased radial (but unchanged axial) diffusion of water. *Neuroimage.* 2002;17(3):1429–1436.
59. Balleine BW, Delgado MR, Hikosaka O. The role of the dorsal striatum in reward and decision-making. *J Neurosci.* 2007;27(31):8161–8165.
60. Jiang W, Shi F, Liu H, *et al.* Reduced white matter integrity in antisocial personality disorder: a diffusion tensor imaging study. *Sci Rep.* 2017;7:43002.
61. Glenn AL, Yang Y. The potential role of the striatum in antisocial behavior and psychopathy. *Biol Psychiatry.* 2012;72(10):817–822.
62. van der Knaap LJ, van der Ham IJ. How does the corpus callosum mediate interhemispheric transfer? A review. *Behav Brain Res.* 2011;223(1):211–221.
63. Glickstein M, Berlucchi G. Classical disconnection studies of the corpus callosum. *Cortex.* 2008;44(8):914–927.
64. Schutter DJ, Harmon-Jones E. The corpus callosum: a commissural road to anger and aggression. *Neurosci Biobehav Rev.* 2013;37(10 Pt 2):2481–2488.
65. Sundram F, Deeley Q, Sarkar S, *et al.*; UK AIMS Network. White matter microstructural abnormalities in the frontal lobe of adults with antisocial personality disorder. *Cortex.* 2012;48(2):216–229.
66. Winston GP. The physical and biological basis of quantitative parameters derived from diffusion MRI. *Quant Imaging Med Surg.* 2012;2(4):254–265.
67. Sedgwick O, Young S, Baumeister D, Greer B, Das M, Kumari V. Neuropsychology and emotion processing in violent individuals with antisocial personality disorder or schizophrenia: the same or different? A systematic review and meta-analysis. *Aust N Z J Psychiatry.* 2017;51(12):1178–1197.
68. Fullam R, Dolan M. Emotional information processing in violent patients with schizophrenia: association with psychopathy and symptomatology. *Psychiatry Res.* 2006;141(1):29–37.
69. Volavka J, Swanson J. Violent behavior in mental illness: the role of substance abuse. *JAMA.* 2010;304(5):563–564.
70. Fazel S, Långström N, Hjern A, Grann M, Lichtenstein P. Schizophrenia, substance abuse, and violent crime. *JAMA.* 2009;301(19):2016–2023.
71. Ozcelik-Eroglu E, Ertugrul A, Oguz KK, Has AC, Karahan S, Yazici MK. Effect of clozapine on white matter integrity in patients with schizophrenia: a diffusion tensor imaging study. *Psychiatry Res.* 2014;223(3):226–235.