Preventing PTSD with oxytocin

Effects of oxytocin administration on fear neurocircuitry and PTSD symptom development in recently trauma-exposed individuals

Frijling, J.L.

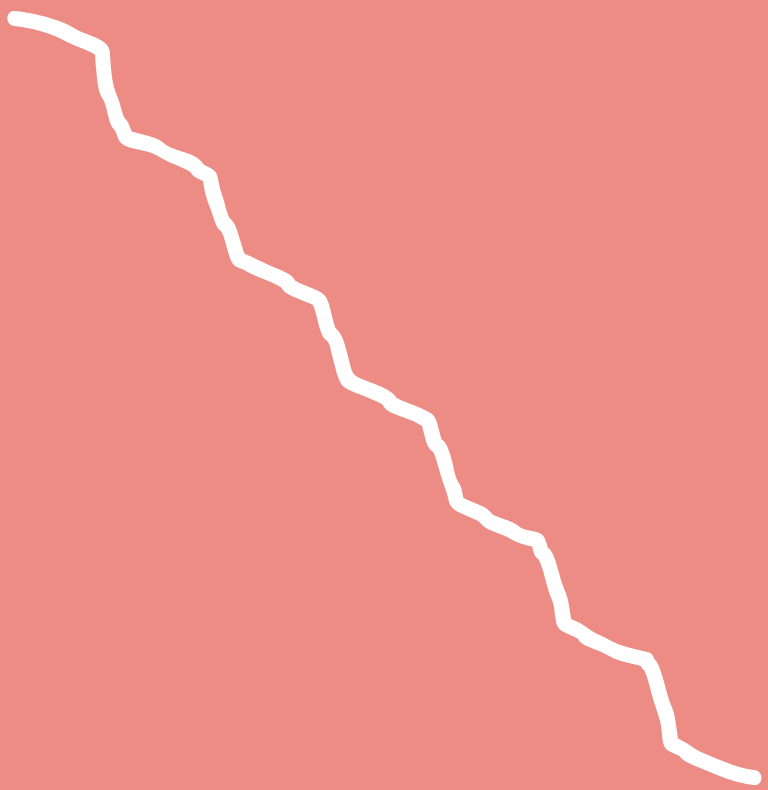
Publication date
2017

Document Version
Other version

License
Other

8

Acute PTSD hyperarousal symptoms are positively associated with white matter integrity of the angular bundle of the left cingulum



Jessie L. Frijling,
Mirjam van Zuiden,
Saskia B.J. Koch,
Laura Nawijn,
Kim Alyousefi–van Dijk,
Dick J. Veltman
and Miranda Olff

Submitted

ABSTRACT

Posttraumatic stress disorder (PTSD) is a common debilitating psychiatric disorder. Knowledge on neural vulnerability factors for PTSD may inform us on which trauma-exposed individuals are at increased risk for PTSD and may provide insights on neural processes etiologically involved in PTSD. In a cross-sectional diffusion tensor imaging (DTI) study in recently trauma-exposed emergency department patients (*n*=42) assessed within 11 days posttrauma, we investigated whether white matter integrity of two white matter tracts connecting areas implicated in PTSD vulnerability (i.e. the bilateral uncinate fasciculus and cingulum) was related to acute PTSD symptom severity. Fractional anisotropy (FA) values of the left cingulum-angular bundle (CAB) were positively associated with acute symptom severity of the PTSD hyperarousal cluster, suggesting that vulnerability for the development of (acute) symptoms of the PTSD hyperarousal cluster is associated with aberrant amygdala-dACC circuitry functioning. This finding is in line with a previously proposed neurocircuitry model of PTSD vulnerability postulating that amygdala and dorsal anterior cingulate cortex (dACC) hyperreactivity is associated with a predisposition towards hyperarousal and PTSD vulnerability.

INTRODUCTION

Approximately 80% of the Dutch general population experiences at least one traumatic event during their lifetime (de Vries and Olff, 2009);. Around ten percent of trauma-exposed individuals develops posttraumatic stress disorder (PTSD) (de Vries and Olff, 2009); a debilitating psychiatric disorder characterized by re-experiencing the traumatic event, avoiding trauma-related stimuli, and alterations in cognitions and mood, as well as in arousal and reactivity (American Psychiatric Association, 2013). As trauma exposure serves as an identifiable event of potential PTSD onset, the acute posttrauma time-period provides opportunity for prevention. Currently, however, there are no preventive early interventions at the stage of widespread implementation. Increasing knowledge on neural vulnerability factors for PTSD may inform us on which trauma-exposed individuals are at increased risk for PTSD. This is relevant as prevention based on individual risk estimation is likely more effective than non-selective prevention. Furthermore, it may also provide insights regarding neural processes etiologically involved in PTSD symptom development. Novel early interventions that target these processes may effectively reduce risk of PTSD development in recently trauma-exposed individuals.

Relating acute PTSD symptoms to neuroimaging data collected pre- or early posttrauma can inform on neural PTSD vulnerability factors. Prospective studies showed that pretrauma higher amygdala reactivity predicted higher PTSD symptoms following trauma exposure in military personnel (Admon et al., 2009) and adolescents exposed to a terrorist attack (McLaughlin et al., 2014). Additionally, combat-exposed veterans with PTSD and their non-exposed twins had higher dorsal anterior cingulate cortex (dACC) reactivity during a cognitive interference task than combat-exposed veterans without PTSD and their non-exposed twins (Shin et al., 2011). A decrease in limbic-ventromedial prefrontal cortex (vmPFC) functional and structural connectivity (i.e. white matter (WM) integrity of the uncinate fasciculus (UF)) over the course of combat exposure coincided with PTSD symptom development in military personnel (Admon et al., 2013a). Based on these findings and on indirect evidence from genetic studies and associations between childhood trauma – a vulnerability factor for adulthood PTSD – and amygdala/dACC function, Admon and colleagues (Admon et al., 2013c) suggested a causal neurocircuitry model for PTSD vulnerability. This model states that pretrauma amygdala and dACC hyperreactivity to emotional stimuli is a PTSD vulnerability factor, whereas aberrant limbic-ventral prefrontal cortex (vPFC) functional and structural connectivity is an acquired neural abnormality in PTSD. However, low regional WM integrity in the vmPFC and ventral ACC (vACC) two days after a traffic accident predicted PTSD at 1 and 6 months posttrauma (Sun et al., 2013), suggesting that aberrant WM integrity in vPFC areas could also be a pre-existing PTSD vulnerability factor instead of an acquired trait.

Individual brain region functioning is affected by the efficiency of communication between brain regions within the same neural circuitry, which is dependent on WM integrity of the tracts connecting these regions. To further study neural correlates of PTSD vulnerability, we used diffusion tensor imaging (DTI) to investigate the relationship between WM integrity and acute PTSD symptom severity in recently trauma-exposed emergency department (ED) patients. We specifically assessed integrity of two WM tracts associated with the above discussed potential neural PTSD vulnerability factors, i.e. the bilateral UF (connecting the vPFC and medial-temporal limbic regions) and the cingulum (connecting the ACC and medial-temporal limbic regions, subdivided into the cingulate gyrus (CCG) and angular bundle (CAB) (previously also described as the posterior or parahippocampal cingulum)).

METHODS

Design, participants and procedures

This cross-sectional DTI study was part of a randomized placebo-controlled functional magnetic resonance imaging (fMRI) study in which effects of intranasal oxytocin administration on functional fear neurocircuitry in recently trauma-exposed individuals were investigated. The study was approved by the Institutional Review Board of the Academic Medical Center (AMC) and conducted following Good Clinical Practice guidelines.

Forty-seven participants (males *n*=20) were scanned after giving verbal and written informed consent. Participants were recruited at three EDs in Amsterdam, the Netherlands, after experiencing a traumatic event according to the DSM-IV PTSD A1 criterion (American Psychiatric Association, 2000). Potentially trauma-exposed ED patients were contacted for screening within 7 days posttrauma (mean(*SD*)=3.2(1.9) days). The presence of peri- and immediate posttrauma distress was assessed using the Peritraumatic Distress Inventory (PDI) (Brunet et al., 2001) (cutoff score≥17) and the Trauma Screening Questionnaire (TSQ) (Brewin et al., 2010) (cutoff score≥5, see (Frijling et al., 2014) for cutoff selection). Dutch or English speaking adults (18-65 years) scoring above the cutoff on the TSQ and/or PDI, and hence with increased PTSD (Frijling et al., 2014), were invited to participate. Exclusion criteria were MRI contraindications; severe/chronic systemic disease; current PTSD, depressive, psychotic, bipolar, substance-related or personality disorder; mental retardation; neurological/endocrinological disorder; ongoing traumatization; medication use potentially interfering with oxytocin (e.g. glucocorticoids, psychiatric medication); allergy for oxytocin; impaired consciousness or amnesia at time of inclusion; pregnancy and breastfeeding.

Within 8 days posttrauma (mean(*SD*)=5.8(1.9) days) current and lifetime psychopathology and acute PTSD symptom severity since the recent trauma were assessed using the MINI international neuropsychiatric interview (MINI) (Sheehan et al., 1998) and clinician-administered PTSD scale (CAPS) (Blake et al., 1995). The DTI scan was acquired within 11 days posttrauma (mean(*SD*)=8.4(2.2) days).

As this DTI study was part of a fMRI study in which effects of intranasal oxytocin administration on functional fear neurocircuitry were studied, prior to scanning, all participants received a single intranasal administration of placebo or 40 IU oxytocin. There is no theoretical or empirical indication that a single oxytocin administration influences WM integrity. Therefore, all analyses were conducted disregarding intranasal treatment.

Scan acquisition

Diffusion weighted and T1-weighted structural brain imaging data were acquired on a 3T MRI scanner (Philips Intera, Philips Medical Systems, Best, the Netherlands) with a 16-channel SENSE head coil. Diffusion-weighted images (DWIs) were acquired using a *b*-value of 1000 s/mm2. Sixty coronal slices were obtained using the following sequence parameters: echo time 92ms, repetition time shortest (6383ms), slice thickness 2mm, field of view 224 x 224 x 120 mm, and voxel size 2mm3. The diffusion weighting was performed along 46 directions. Total DTI scan time was 6 minutes and 47 seconds. T1-weighted images were acquired using a 3D magnetization-prepared rapid acquisition with gradient echo (MPRAGE) sequence (TR=6.7ms; TE=3.1ms; matrix size 256x256; voxel size 1.11x1.11; flip angle=9; 170 sagittal slices).

Data processing

See for details on data processing the supplementary methods. In short: preprocessing of DWIs and subsequent probabilistic tractography of our tracts of interest was partly conducted with in-house developed software, executed on the Dutch e-science Grid (http://www.biggrid.nl), with a web-interface to the e-Bioinfra gateway (Shahand et al., 2015). After preprocessing, we used TRACULA (TRActs Constrained by UnderLying Anatomy) for global probabilistic tractography (Yendiki et al., 2011). The estimated diffusion probability distributions as provided by BedPostX and (sub)cortical segmentations as provided by FreeSurfer 5.3 based on T1-weighted images were used by TRACULA (step 3 only) to automatically reconstruct the bilateral UF, CAB and CCG (Figure 8.1 (Yendiki et al., 2011)). Average weighted FA-values for each reconstructed tract were used in the analyses.

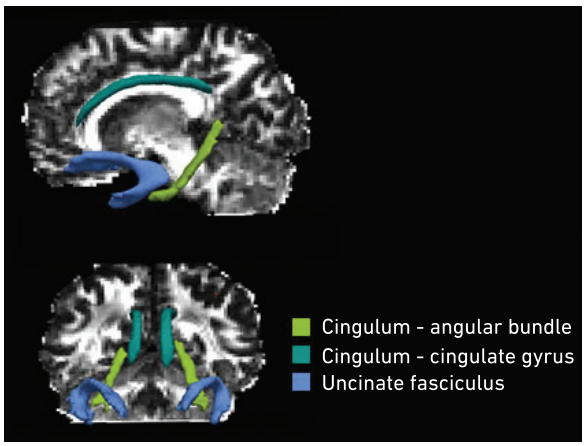
Statistical analyses

Five participants were excluded from the analyses due to technical errors during scanning (*n*=2), motion artifacts (*n*=1) and early discontinuation of the scan protocol (*n*=2), leading to a total of 42 participants (males *n*=17) included in the analyses. All statistical analyses were performed in SPSS 23.0 (IBM, Armonk, NY, USA). Distributions of all continuous variables were checked for normality (i.e. standardized skewness >2.58 and/or standardized kurtosis >2.58). FA-value of left CCG initially was non-normally distributed but removal of one outlier (i.e. *z*-score >2.58) resulted in a normal distribution.

The relationships between the extracted mean FA-values for each tract (bilateral UF, CAB and CCG) and acute PTSD symptom severity as assessed within 8 days posttrauma (CAPS total scores and CAPS subscales) were assessed with linear regression analyses. Age was included as covariate since prefrontal WM integrity may decrease with age (Sexton et al., 2014). Considering the high correlation between the four acute PTSD symptom severity measures (i.e. CAPS total score and subscales), the alpha of 0.05 was false discovery rate (FDR)-corrected for multiple testing (Benjamini and Hochberg, 2016).

To assess whether observed significant associations between acute symptom severity and WM integrity were not confounded by lifetime history of PTSD, significant associations were followed-up by linear regression analyses additionally including lifetime history of PTSD. Lifetime history of PTSD was missing for one participant.To maintain statistical power, the missing value was imputed (discrete series mean).

Figure 8.1



Tracts of interest. Trajectories of the uncinate fasciculus (UF), cingulum-cingulate gyrus (CCG) and cingulum-angular bundle (CAB) of a representative participant.

Table 8.1 Participant characteristics.

	Mean / *n*	*SD* / %
N	*n*=42	-
Male	*n*=17	40.5%
Age	31.5	11.2
Trauma type		
Traffic accident	*n*=25	59.5%
Work/home accident	*n*=7	16.7%
Interpersonal trauma	*n*=9	21.4%
Other	*n*=1	2.4%
PDI	21.6	6.2
TSQ	6.0	2.4
CAPS total since trauma	42.7	19.4
CAPS re-experiencing	17.0	9.0
CAPS avoidance	10.2	6.6
CAPS hyperarousal	15.5	7.8
Lifetime history of PTSD	*n*=5*	12.2%
Time since trauma at scanning (days)	8.4	2.2
Time since trauma at acute PTSD symptom assessment (CAPS) (days)	5.8	1.9

CAPS Clinician-administered PTSD scale; HADS-D Hospital anxiety and depression scale, depression subscale; PDI Peritraumatic distress inventory; PTSD Posttraumatic stress disorder; TSQ Trauma screening questionnaire. *missing for one participant.

RESULTS

Participant characteristics

Participants' demographics, trauma type, lifetime history of PTSD, and acute symptom severity measures (means + SDs) are listed in Table 8.1.

Relationship between FA-values and acute PTSD symptom severity

The linear regression analyses showed higher FA-values in the left CAB were significantly associated with higher acute CAPS hyperarousal scores (beta=0.39, t=2.745, p=.009 (FDR-corrected alpha=0.0125)), and were nominally significantly associated with acute total CAPS scores after FDR-correction for multiple comparisons (beta=0.33, t=2.275, p=.028 (FDR-corrected alpha=0.025)). The positive association between left CAB FA-values and acute CAPS hyperarousal scores remained significant when additionally adjusting for lifetime history of PTSD (p=.007). Age was not significantly associated with acute CAPS total or subscale scores, and lifetime history of PTSD was not significantly associated with acute CAPS hyperarousal scores (p-values>.05). There were no significant associations between FA-values of our other tracts of interest and acute PTSD symptom severity measures.

DISCUSSION

In recently trauma-exposed ED patients, we investigated the relationship between acute PTSD symptoms and WM integrity of the bilateral UF and the cingulum (CAB and CCG) within 11 days posttrauma. Using probabilistic tractography methods, we demonstrated that WM integrity of the left CAB was positively associated with acute symptom severity of the PTSD hyperarousal cluster. This finding remained significant after adjusting for lifetime history of PTSD. As acute PTSD symptoms predict subsequent PTSD development (e.g. Classen et al., 1998), aberrant WM integrity of the left CAB may reflect a neural correlate of PTSD vulnerability.

The neurocircuitry model of PTSD vulnerability of Admon and colleagues postulates that PTSD vulnerability is related to (pre-existing) hyperreactivity of the amygdala and dACC and disrupted connectivity within amygdala-dACC circuitry (Admon et al., 2013c). Given the important role of the amygdala-dACC circuitry in fear generation and expression, Admon et al. hypothesized that pre-existing amygdala-dACC dysfunction results in a predisposition to hyperarousal symptoms (i.e. irritability, exaggerated startle and hypervigilance). The suggested relationship between (pretrauma) hyperarousal and PTSD vulnerability is further supported

by studies in police recruits demonstrating that higher startle responses assessed prior to police training predicted higher PTSD symptoms after police training (Pole et al., 2009). In ED patients, more severe hyperarousal symptom severity within several days posttrauma was associated with slower subsequent decline of PTSD symptoms (Schell et al., 2004). Our finding that acute symptom severity of the PTSD hyperarousal cluster was specifically associated with WM integrity of the cingulum further adds to the hypothesis of the relationship between hyperarousal symptoms, amygdala-dACC circuitry and PTSD vulnerability. Furthermore, the lack of a significant association between acute PTSD symptoms and WM integrity of the UF is also in line with the previously proposed neurocircuitry model of PTSD vulnerability, as Admon et al. (2013c) suggested that aberrant hippocampal-vPFC connectivity constitutes an acquired neural correlate of PTSD, not a PTSD vulnerability factor (Admon et al., 2013c).

Lower FA-vales of the left CAB were previously observed in PTSD patients compared to controls (Fani et al., 2012). However, the CAB has never been specifically studied in recently trauma-exposed individuals. Indirect evidence from a sample of highly trauma-exposed women with and without PTSD indicated that carrying two risk alleles of an FKBP5 single nucleotide polymorphism (a PTSD vulnerability factor (Binder et al., 2008) was associated with lower FA-values in the left CAB (Fani et al., 2013). Our observed positive association between acute symptom severity of the PTSD hyperarousal cluster and WM integrity of the left CAB appears at odds with these previous findings indirectly linking lower WM integrity of the CAB to PTSD (vulnerability). This discrepancy may be related to differences in population and outcome measures (PTSD diagnosis at follow-up (Sun et al., 2013) vs acute PTSD symptoms; genetic marker as vulnerability factor (Fani et al., 2013) vs acute PTSD symptoms as vulnerability factor).

This is the first study using hypothesis-driven tractography to assess the relationship between WM integrity and acute PTSD symptoms, which is relevant as pre- and early posttrauma neuroimaging studies informing on neural PTSD vulnerability are scarce and DTI studies in recently trauma-exposed individuals are limited. However, some limitations need to be mentioned. As we did not include a non-trauma-exposed control group and did not acquire pretrauma DTI scans, we could not investigate effects of trauma-exposure on WM integrity. Although it was previously demonstrated that there were no differences in FA-values between individuals assessed two days after a car accident who subsequently did not develop PTSD and non-trauma-exposed controls (Sun et al., 2013) – suggesting that trauma exposure alone does not influence WM integrity early posttrauma – the temporal dynamics of the presence or development of PTSD symptoms affecting WM integrity remain unclear. Additionally, we did not have sufficient prospective clinical outcome measures available to directly test whether acute posttrauma WM integrity and acute PTSD symptoms predicted subsequent PTSD symptoms. This should be tested in future prospective studies in order to further investigate

Table 8.2 Age-adjusted results of linear regression analyses of FA-values of white matters tracts and acute PTSD symptom severity.

White matter tract		Acute PTSD symptoms (clinician-rated)	*Beta*	*t*-score	*p*-value
Uncinate fasciculus	Right	CAPS total	-0.06	-0.36	.719
		CAPS re-experiencing	-0.20	-1.31	.197
		CAPS avoidance	0.08	0.51	.614
		CAPS hyperarousal	0.02	0.14	.890
	Left	CAPS total	0.03	0.19	.847
		CAPS re-experiencing	-0.08	-0.49	.627
		CAPS avoidance	0.30	1.89	.066
		CAPS hyperarousal	-0.08	-0.52	.604
xCingulum - cingulate gyrus	Right	CAPS total	-0.08	-0.49	.630
		CAPS re-experiencing	-0.03	-0.19	.847
		CAPS avoidance	-0.06	-0.40	.689
		CAPS hyperarousal	-0.10	-0.63	.535
	Left	CAPS total	-0.08	-0.53	.602
		CAPS re-experiencing	-0.11	-0.70	.486
		CAPS avoidance	0.02	0.14	.893
		CAPS hyperarousal	-0.10	-0.61	.543
Cingulum - angular bundle	Right	CAPS total	0.23	1.48	.147
		CAPS re-experiencing	0.22	1.45	.156
		CAPS avoidance	0.16	1.02	.313
		CAPS hyperarousal	0.17	1.09	.284
	Left	CAPS total	0.33	2.27	.028#
		CAPS re-experiencing	0.20	1.30	.203
		CAPS avoidance	0.24	1.55	.128
		CAPS hyperarousal	0.39	2.75	.009*

* Statistically significant result after FDR-correction (alpha=0.0125); # Non-significant after FDR-correction. FDR False discovery rate; CAPS Clinician-administered PTSD scale.

neural vulnerability factors for PTSD. Sample sizes of such studies should be sufficient to assess mediating and/or moderating factors, such as pre-existing hyperarousal symptoms, and childhood trauma. Furthermore, as acute PTSD symptoms and mild traumatic brain injury (mTBI) – which we did not take into account – are both associated with increased PTSD risk, cognitive dysfunction and early posttrauma aberrant brain function and structure (Eierud et al., 2014), common and distinct neural characteristics of mTBI and vulnerability factors for PTSD should be investigated. Finally, novel psychological or pharmacological interventions that modify processes associated with structural connectivity of the CAB (i.e. fear generation, fear learning) may be investigated as early posttrauma preventive interventions for PTSD.

In conclusion, we observed a positive association between early posttrauma WM integrity of the left CAB and acute PTSD hyperarousal symptoms. This suggests that vulnerability for development of (acute) symptoms of the PTSD hyperarousal cluster is associated with aberrant amygdala-dACC circuitry functioning, as was also postulated in the previously proposed neurocircuitry model for PTSD vulnerability (Admon et al., 2013c). Prospective neuroimaging studies are needed to further unravel neural correlates of PTSD vulnerability, possibly leading to novel targets for preventive interventions for PTSD.

AUTHOR DISCLOSURES

Acknowledgements

We thank all emergency department patients who were willing to participate in the initial screening, and in the study. We thank J.C. Goslings, J.S.K. Luitse, T. Biesheuvel, E. Hofstra, F.C. Bakker, A. Honig, P. Philipse, and R. Van Nieuwenhuizen, as well as all other emergency department and trauma surgery department personnel for their hospitable and helpful attitude towards our study at their departments. We thank Joanne Will and Annike Bekius for scanning assistance, and other students involved in the study for their assistance in recruitment and assessment procedures.

Role of funding sources

This study was funded by grants from the Netherlands organization for Health research and Development (ZonMw, grant no. 91210041) and from the AMC Research Council (grant no. 110614). All funding sources had no further role in designing the study; in the collection, analysis, and interpretation of data; in writing the report; or in deciding to submit the paper for publication.

Contributors

MO designed the study. JLF and MvZ drafted the manuscript. JLF, MvZ, LN, SBJK, DJV and MO contributed to the development and implementation of the study protocol. JLF, LN, SBJK and KA-vD conducted all participant-related study procedures and data collection. JLF and KvD processed and analyzed the data. All authors contributed to editing the manuscript and read and approved the final manuscript.

Conflict of interest

All authors declare that they have no conflicts of interest.

SUPPLEMENTARY METHODS

Data processing

Preprocessing of diffusion weighted images (DWIs) and subsequent probabilistic tractography of our tracts of interest were similar to previous work(Koch et al., n.d.)). Preprocessing of the DWIs was conducted with in-house developed software, programmed in Matlab (The Mathworks, Natick, MA) and executed on the Dutch e-science Grid (http://www.biggrid.nl), with a web-interface to the e-Bioinfra gateway (Shahand et al., 2015). Head movement and deformations induced by eddy currents were corrected for using affine registration of the DWIs to the non-diffusion weighted image. The gradient directions were corrected by the rotation component of the transformation. The DWIs were resampled isotropically. Rician noise was reduced with an adaptive noise filtering method for higher precision of diffusivity values (Caan et al., 2010). Voxel-wise probability distributions of the diffusion direction were estimated on the preprocessed DWIs using the ball-and-stick model in BedPostX (Bayesian Estimation of Diffusion Parameters obtained using sampling techniques) (Behrens et al., 2007) of FSL (Functional Software Library), also executed on the Dutch e-science Grid. Automated cortical and subcortical segmentation of the structural T1-weighted scan was performed with Freesurfer version 5.3, using default options (Fischl, 2013).

After preprocessing, we used TRACULA (TRActs Constrained by UnderLying Anatomy) for global probabilistic tractography(Yendiki et al., 2011). The estimated diffusion probability distributions as provided by BedPostX and (sub)cortical segmentations as provided by FreeSurfer were used by TRACULA (step 3 only) to automatically reconstruct the bilateral UF, CAB and CCG (Figure 8.1 (Yendiki et al., 2011)). Additional preprocessing in TRACULA included intrasubject registration of DWIs to the structural T1-weigthed image, intersubject registration of structural T1-weighted images to a template space, creation of cortical and WM masks from FreeSurfer reconstructions and tensor fitting for extraction of tensor-based measures (i.e. FA-values). Finally, anatomical priors for the WM pathways were computed from the TRACULA atlas, consisting of manually reconstructed WM tracts in 30 healthy individuals. For each subject, WM tracts were reconstructed by simultaneously fitting the shape of each pathway to the individual diffusion probability distributions and to the anatomical priors based on the TRACULA atlas (using TRACULA default settings, e.g. number of control points and permutations). Average weighted FA-values for each reconstructed tract were used in the analyses.